EDINBURGH POST-GRADUATE LECTURES IN MEDICINE

VOLUME SEVEN

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FOREWORD

THIS volume includes a series of lectures delivered in the Royal Infirmary Edinburgh under the auspices of the Honyman Gillespie Trust and the Edinburgh Post Graduate Board for Medicine A generous grant in support of post graduate medical education was originally made by the Trustees of the late Mrs Honyman Gillespie some time before the last War In 1937 the Committee responsible for post graduate medical education in Edinburgh with this object in view established a series of post graduate lectures which have been continued each year during the teaching terms A representative committee with the Chairman of the Post Graduate Executive Committee now the Edinburgh Post Graduate Board for Medicine as Convener arranges the annual programme and selects the lecturers from amongst those who can speak with authority and from experience on their particular subjects The lectures are open to all medical men and senior students but are specially intended to be helpful to the large number of graduates attending the courses on internal medicine and on surgery during the teaching terms

The Honyman Gillespie lectures have been published in the *Edinburgh Medical Journal* and later have been collected together in volumes of which this is the seventh to appear Over 220 lectures on a great variety of medical and surgical subjects have now been delivered and published The Committee hope that this volume the last of the present series will be welcomed as a contribution to medical knowledge and as a record of the experience and teaching of members of the Edinburgh Medical School

J M GRAHAM
Chairman of Committee

The Committee which nominates and invites the lecturers consists of the Professor of the Practice of Medicine Systematic Surgery and Obstetrics in the University the Presidents of the Royal College of Physicians and of the Royal College of Surgeons the Senior non professional Physician and Surgeon on the Staff of the Royal Infirmary the Editor of the *Edinburgh Medical Journal* the Director of Post Graduate Studies and the Chairman of the Edinburgh Post Graduate Board for Medicine as Convener

SOME ASPECTS OF MITRAL DISEASE IN RELATION TO SURGICAL TREATMENT

By D M DOUGLAS M B E M B Ch M M S F R C S Ed and Eng
Professor of Surgery University of St Andrews
and
IAN G W HILL C B E T D M B F R C P Ed M R C P Lond F R S E
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PART I

Medical Aspects

A YEAR or two ago after addressing a medical society in a Scottish city I was somewhat taken aback to be asked why it was that medical diagnosis became so much more accurate whenever the surgeons took a hand in treatment of a disease? It is certainly true in respect of the diagnosis of congenital cardiac anomalies the topic on which I had been speaking that night and it applies no less to the case of mitral stenosis The skill and daring of our surgical colleagues now afford a prospect of dramatic relief for many victims of this hitherto grim and inexorable disease and it has become imperative for the physician to attain a precision in diagnosis and assessment which previously had seemed unnecessary Further studies of the lesser circulation in those afflicted with mitral disease have opened up a vast unexplored territory —from which the first explorers bulletins have at once served to explain many hitherto little understood phenomena in the natural history of cardiac disease and have at the same time revealed our fundamental ignorance of the physiology of the pulmonary circulation alike in health and disease All over Europe and America work is being feverishly prosecuted along the new lines at the First European Congress of Cardiology in London in 1952 no less than 30 papers from ten European countries were devoted to the problems of mitral disease particularly in relation to surgery Well documented careful work on large series of surgically treated cases has appeared in this country from various centres—from the group at Guy s Hospital who were pioneers in Britain in this field (Baker *et al* 1952) from Logan and Turner (1952 1953) in Edinburgh and recently from the Middlesex Hospital team (Sellors *et al* 1953)

Read 26th November 1953

It may seem presumptuous for us to night to present our relatively modest series of cases particularly since our experience parallels closely that of others On the other hand there may be some advantage in presenting an admittedly limited personal experience to an audience with wide interest such as this The day is past when consideration of mitral valvotomy was a matter purely for cardiologists, it is now, as I hope to show a matter for urgent consideration by all physicians having charge of mitral patients The general physician can and must learn to assess for himself the suitability of individual patients for operation without recourse to the complicated procedures of a cardiac clinic

THE MAGNITUDE OF THE PROBLEM —There is still widespread lack of appreciation of the magnitude of the rheumatic *cardiac* problem in this country though the ravages of articular rheumatism are fully recognised It is fitting that I should here acknowledge the contribution of W T Ritchie one time Professor of Medicine in this school a teacher and physician to whom I personally owe much, who in 1936 published his 'crusade against rheumatism' (Ritchie, 1936) drawing attention to the prevalence and ravages of this scourge More recently Parkinson (1945) in a Harveian oration has given a vivid account of the incidence of rheumatic heart disease Basing his calculation on the facts that of 6½ million men between 18 and 41 years of age called up for service during the 1939-45 war, about one million were found medically unfit while in a representative sample of 30,000 rejections 9 per cent were due to cardiac disease Parkinson reckons that there must be about 100 000 cases of rheumatic heart disease among *men* in this age group in England and Wales Taking account of the incidence in women in Scotland and in the large population of men not medically examined we have an estimate of 300 000 victims in this adult age group in Britain Further he adduces evidence that the annual death rate from rheumatic heart disease in England and Wales alone is of the order of 16 000 If we assume that only half of these doomed patients are suffering from mitral stenosis and that again only half of these are suitable for surgical treatment we still have an estimated 4000 cases a year who are candidates for operation These figures tally with those of Wood (1952) Translated into terms of man power, this represents two operations per week throughout the year for each of nearly forty surgeons If operation is to be restricted to those who can be investigated in detail in specialised cardiac departments then the benefits of operation are to be denied to thousands of hapless victims each year On the other hand if operation is to be advised in individual cases by general physicians it is imperative that the criteria of suitability should be carefully studied, otherwise grave harm may result

Such are the apologia which one advances in mitigation of one s temerity in addressing you on this subject to night

NATURAL HISTORY OF MITRAL STENOSIS —In the fields of zoology

and botany the emphasis in the present century has swung rather away from taxonomy and classification to ecological studies So too in medicine we see a parallel orientation of interest in the natural history of disease pioneered by Ryle and his colleagues, and exemplified most recently by the work of Morris *et al* (1953) on coronary disease (See also Morris 1952) If we consider for a moment the usual march of events in the subject of mitral stenosis we may recall the variable latent period which may intervene between the occurrence of acute rheumatic infection and that of cardiac symptoms, the usual gradual progression of exertional dyspnœa the eventual onset of auricular fibrillation and failure the bouts of congestive failure responding at first to rest and medication, recurring at progressively shorter intervals and with slower response to treatment till finally intractable failure leads to death It is I think not without significance that Cushny, the world authority of his day on Digitalis and its Allies (Cushny, 1926) should have chosen to emblazon on the walls of his lecture theatre in bold Gothic blackletter of heroic size the legend "Contra Vim Mortis Non Est Medicamen in Hortis The therapeutic helplessness of the physician in face of the terminal stages of mitral disease is strong argument for seeking surgical relief before this extremity is reached

The downhill path of the average patient is however beset by pitfalls and precipices—pitfalls such as cardiac failure provoked by infection, auricular fibrillation or pregnancy from which rescue is possible by skilled therapy and precipices over which a slip spells permanent disablement or death as cerebral embolism or pulmonary œdema And always poised overhead is the threat of subacute bacterial endocarditis which like the avalanche in the high Alps dislodged by a careless shout may overwhelm the victim on the slight provocation of a careless tooth extraction

Some patients live to advanced years with little progressive disability (Cookson 1949) and run embolic and other hazards with impunity Others a very considerable proportion die of recurrent carditis within a decade of the first rheumatic infection in childhood (Findlay, 1931) The majority run the course outlined above and Wood (1952) has shown that from the first major handicap to total incapacity usually seven years elapse

One major hazard of the disease has attracted attention in this country only during the last decade—acute pulmonary œdema The French cardiologists have recognised it as the œdematous form for many years and looking back one recollects instances many years ago in one s own experience not fully appreciated at the time Alarming attacks of paroxysmal dyspnœa going on it may be to frank pulmonary œdema and very comparable clinically to the familiar cardiac asthma of left ventricular failure have been recently and widely recognised as not uncommon in mitral stenosis and of life threatening danger particularly in pregnancy (Bramwell 1953

Jones 1952) It is a threat particularly to the patient with a tight stenosis a small heart and regular rhythm rather than to the older patient with gross enlargement auricular fibrillation and generalised venous congestion In fact I saw it produced twenty years ago in Vienna by an ill advised restoration of normal rhythm with quinidine in a young woman, who fortunately relapsed into auricular fibrillation losing her alarming dyspnœa and cough with the development of hepatic enlargement and dependent œdema Such attacks remained mysterious till very recently when the unexpected findings of cardiac catheterisation revealed the mechanism

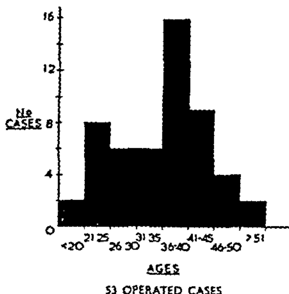


FIG 1 —Age distribution of 53 operated cases of mitral stenosis Nearly 50 per cent were between 36 and 45 years old

INDICATIONS FOR OPERATION —Operative treatment should, I believe be considered in practically every patient with mitral stenosis In many a decision against operation is readily reached For example, operation is uncalled for in individuals with slight or no disability resulting from their lesion Again it is impracticable in those in the terminal stages of their career with gross cardiac enlargement intractable failure and obvious and significant associated valvular disease But in the wide range between those extremes operation as a possibility must be considered and assessed individually It is in the grossly handicapped individual the man who cannot follow his employment the housewife unable to care for her family the woman of child bearing age with a history of previous stormy pregnancies and above all in the individual who is in general little handicapped but has experienced one or more terrifying attacks of paroxysmal dyspnœa—in such patients operation if feasible offers a prospect of relief which *no medical treatment can rival*

The individual must however not only be markedly or grossly

handicapped but must have features suggesting a dominant stenosis of the mitral valve a heart of reasonable size failure if present must have been controlled, and preferably they should be beyond the age at which rheumatic relapse is likely (though biopsy studies and the known relapses which occur in even middle aged patients after operation cast doubt on this proviso)

MATERIAL —Our small series consists of 68 patients of whom 53 have been subjected to operation and are included in my colleague's series about to be reported The chart (Fig 1) shows the age distribution of the cases sent for operation it will be noted that all but 4 lay in the range 21 50 and nearly half (25 out of 53) in the decade 36 45

Most of the individuals were severely or grossly handicapped (36 in cardiac grades IIb or III) of the remainder though physical disability was only moderate when assessed most had a history of failure or of pulmonary œdema or of systemic embolism which appeared to us to justify the risk inherent in cardiac surgery The frequency of certain such episodes in our series is tabulated below —

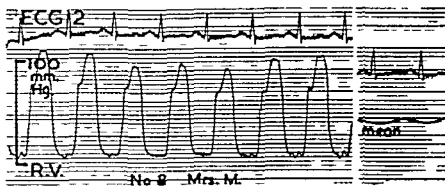
Nocturnal dyspnœa	28 = 50 per cent
Pulmonary œdema	7 = 13
Hæmoptysi	31 = 60
Systemic embolism	14 = 25
Past failure	14 = 25
of which 5 in pregnancy (10 per cent)	

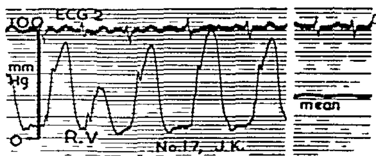
CARDIAC CATHETERISATION —Catheterisation of the right heart and pulmonary artery has been carried out on the majority of the patients in this series the manœuvre failed in a few instances and was not attempted in cases in which the risk appeared greater than normal or when indications of grossly raised right heart pressure were clear Apart from transient ventricular extrasystolic arrhythmias in some patients the procedure was uneventful in all Mild local phlebo thrombosis developed in a few individuals lasting a few days but other sequelæ were not observed The development it may have been fortuitously of pulmonary infarcts in two individuals some days after catheterisation led us to abandon the recording of wedge pressures as a routine particularly since the information yielded by the traces was disappointing In one patient the delay in operation of a few days occasioned by the catheterisation and by pressure of general work in the surgical ward was responsible for the development of a fatal attack of pulmonary œdema Such deaths in patients threatened by pulmonary œdema awaiting operation have been reported from other clinics and we do not now delay a moment longer than is necessary to get the patient into as fit a state as possible for operation

The pressures in our clinic are recorded photographically on a 4 channel Elmqvist electrocardiograph simultaneously with any desired ECG lead The pressure recording system is the Minirack electronic device calibrated repeatedly throughout the procedure



Fig 2—Right ventricular pressure curves and ECG (lead II) in a boy of 18 years with advanced mitral stenosis and auricular fibrillation





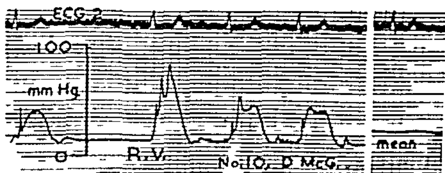


Fig 3—Right ventricular pressure curves and ECG (lead II) in 3 patients with mitral stenosis Note the relatively low pressure in case no 10 who at operation had a tight mitral stenosis

against a mercury manometer * Examples of the tracings (Figs 2, 3) obtained will suffice to illustrate the astonishing pressure which the

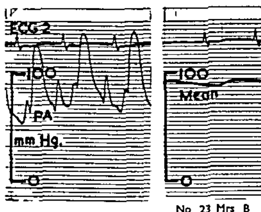


FIG 4—Pulmonary artery pressure curve from a patient with advanced mitral stenosis Her systemic systolic blood pressure was 134 mm Hg that in her pulmonary artery over 140 mm Hg

right ventricle may develop in cases of mitral stenosis In some the pulmonary artery pressure at rest is actually higher than the systolic systemic pressure (Fig 4) In others relatively low pressures may be found within or just above the normal range When we chart the right ventricular pressures against the cardiac grade of incapacity (Fig 5) one sees that very high pressures were found only in individuals with marked or gross disability but a significant proportion of such gravely handicapped people had practically normal resting pressures So also when the pressures are charted against the occurrences of nocturnal dyspnœa or hæmoptysis a large number were found to be normal or little raised

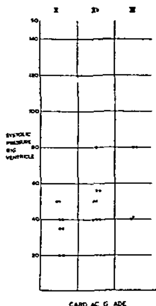


FIG 5—Right ventricular systolic pressure in individual cases arranged according to degree of incapacity (cardiac grade)

The height of the pulmonary arterial pressure in mitral stenosis varies through a wide range in response to exertion and emotion A simple pedalling exercise against slight manual resistance may produce a rise from 50 100 mm Hg which persists it may be for many minutes (Fig 6) Similarly emotional stress may be reflected in a dramatic rise in the pulmonary arterial pressure as in the young

* The ECG 1 monitored throughout on a split beam cathode ray oscilloscope on which pres ure tracings can be simultaneously visualised by using the other channel

man whose pulmonary arterial blood pressure rose from 40 to 100 mm Hg when one of my colleagues was explaining to him about the exercise we proposed (Fig 7) It is significant that this patient presented with paroxysms of dyspnœa and hæmoptysis with radiological features of acute pulmonary congestion fading in a few days with treatment

If the pressure is measured in a catheter wedged into a fine pulmonary arterial twig, the so called pulmonary capillary pressure it is always considerably lower than that in the pulmonary artery There

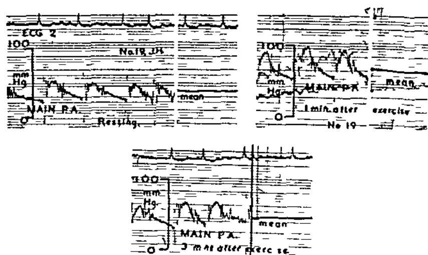


FIG 6—ECG (lead II) and pulmonary artery pressure at rest and after slight exercise in a patient with mitral stenosis

is a gradient therefore across the arteriolar barrier and it is apparent that the pulmonary hypertension in mitral stenosis is only in part a reflection of obstruction at the mitral valve and in larger measure an active hypertension from over activity of the right ventricle and pulmonary arteriolar constriction The pathological and radiological features of this arteriolar barrier are described respectively by Henry (1952) and by Goodwin *et al* (1952) Since the sole factor preventing the transudation of fluid from pulmonary capillaries to alveoli is the plasma protein osmotic pressure of about 35 mm Hg it is apparent that individuals with grossly elevated pulmonary capillary pressures live in a highly dangerous condition The pulmonary arterial pressure may vary widely with little immediate danger but let the pulmonary capillary pressure rise by a few mm and pulmonary œdema ensues at once (Fig 8) In this lies the mechanism of the dangerous attacks referred to above

In view of the instability of the right ventricle and pulmonary artery pressures and the fact that normal or slightly raised values only may be recorded in gravely handicapped subjects I do not believe that such random pressure readings are of any value in deciding for or against operation

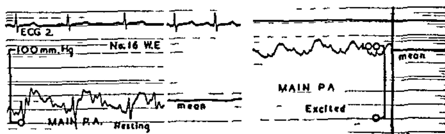


FIG 7—Dramatic rise in pulmonary arterial pressure with emotion in a young man with mitral stenosis and incompetence Clinically he presented with repeated attacks of severe dyspnœa and hæmoptysis showing radiological features in the attacks of acute pulmonary congestion

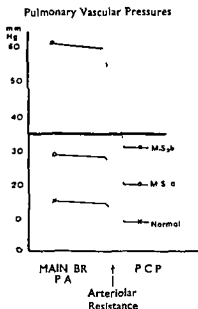


FIG 8—Mean pulmonary arterial pressure and pulmonary capillary pressure showing arterial capillary gradient in normal individuals and in patients with mitral stenosis In mitral stenosis (*a*) the pulmonary arterial is moderately raised in mitral stenosis (*b*) grossly raised The heavy abscissa at 35 mm Hg pressure indicates the critical level—that of the plasma osmotic pressure

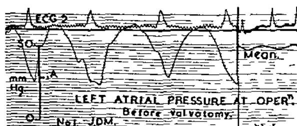


FIG 9—Mid systolic rise of pressure in left atrium recorded by needle puncture at operation in a case of mitral stenosis and incompetence

In some clinics the form of the pulse wave in pulmonary capillary pressure tracings has been thought to afford guidance as to the presence of significant mitral incompetence (Wade *et al* 1952, Wood 1952), but its value is by no means generally accepted A rise of left atrial pressure in mid systole occurs with mitral regurgitation (Fig 9) and is held by some to be transmitted back through pulmonary veins and capillaries to a wedged catheter' In our hands such wedged catheter tracings have not proved of value Wiggers (1953) in a recent review summarises the physical and physiological arguments and evidence

From readings of pulmonary arterial pressure pulmonary capillary pressure and measurement of cardiac output by the Fick principle attempts have been made to calculate the relative roles of mitral obstruction and pulmonary arteriolar resistance in mitral stenosis cases, and even by ingenious hydrodynamic formulæ to calculate the cross sectional area of the mitral orifice (Gorlin and Gorlin 1951) Wiggers (loc cit) arguments in respect of the fallacies of such calculations appear unanswerable

The crucial assessment to be made in cases deemed otherwise suitable for operation is the presence and degree of mitral regurgitation complicating the stenosis Though attempts of great ingenuity and technical brilliance have been made (Logan and Turner 1952) to repair incompetent mitral valves there is no doubt that gross reflux is generally intractable by conventional surgery and its presence militates against a successful operative result

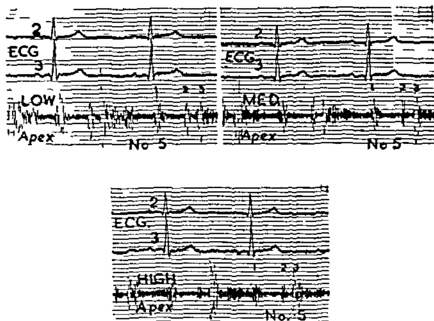
How can we assess then the presence and degree of mitral incompetence? Our feeling in common with others (Venner and Holling 1953 Wade *et al* 1952 Biorck *et al* 1952) is that clinical signs are probably the most reliable guide—not note the traditional systolic murmur only but the position and nature of the apex impulse the quality of the mitral first sound and the nature quality intensity and duration of any systolic murmur

The diffuse short lived tapping impulse of right ventricular hypertrophy as opposed to the localised slow heave of the displaced apex of left ventricular hypertrophy the loud short slapping quality of the mitral first sound clear cut decisive if a systolic murmur is present its faintness high pitch and short duration as opposed to the loud rough long blow of mitral incompetence—all these are clinical points of importance Much has been written of the opening snap a high pitched additional sound heard best medial to the apex early in diastole it has been said to be diagnostic of stenosis and absent in incompetence Its timing has been precisely defined (Mounsey 1953) with phonocardiographic aid but one doubts whether the clinician can possibly time to a nicety events whose range of incidence overlaps and whose average difference in timing is no more than 12/100 second In any case one personally doubts the reliability of the sign—an example (Fig 10) is figured of a high pitched extra sound

occurring 0·15 second after the second sound in a case of proven marked mitral incompetence

Radiology is an indispensable part of the pre operative investigation and has much to teach us The clinical impression of heart size can be checked the respective degrees of right and left ventricular hypertrophy assessed the size of the left atrium determined and pulmonary congestion visualised Valvular calcification is seen in many patients though in this series only in about half of those in whom it was encountered at operation—9 and 6 respectively

So-called MITRAL OPENING SNAP



At operation Mitral Incompetence 1 in orifice

FIG 10—Simultaneous ECGs (leads II and III) and apical phonocardiogram in a patient with mitral disease A loud high pitched extra sound 0·15 second after the second heart sound is visible in all traces and very obvious in the high frequency record At operation mitral incompetence with a gaping 1 inch orifice was found

The significance of systolic expansion of the left atrium has been debated at length In our experience as with Venner and Holling (1952) this sign has not proved of value Systolic expansion of the left atrium may occur in the absence of mitral incompetence and is often absent when mitral incompetence is subsequently proved at operation In one instance we were so impressed by the immobile left atrium at operation in a patient with a gross regurgitant jet that we called for our colleague the radiologist to see matters for himself If pulsation cannot be seen in the exposed atrium in the glare of full theatre lighting how can it be relied on in the shadows of a fluorscopic twilight?

In summary radiology is of great value but seldom affords reliable *direct* guidance of mitral incompetence

So too the ECG may yield permanent records of rhythm or of atrial hypertrophy and may give evidence of left ventricular hypertrophy By contrast with the right ventricular hypertrophy of congenital heart disease however the ECG is relatively unhelpful in diagnosis of right ventricular hypertrophy in mitral stenosis (Fraser and Turner, 1953) The right axis shift in standard leads is often due to rotation of a vertical heart and may be unaccompanied by signs of right ventricular hypertrophy in the precordial leads

OPERATIVE FINDINGS

CLINICAL DIAGNOSIS	M.S. PURE	M.S. M.I	M.S. M.I	M.I. M.S	M.I. PURE
M.S. PURE	• •				
M.S/M.I					
M.S. M.I					
M.I. M.S					

CORRELATION OF CLINICAL DIAGNOSIS AND OPERATIVE FINDINGS

FIG 11 —Correlation of clinical diagnosis and operative findings The clinical diagnosis as shown in the left hand column was confirmed or refuted by the findings at operation as shown by the dots in the five remaining columns Agreement of clinical and surgical diagnosis is represented by the heavy rectangles

We are driven back therefore to clinical assessment as our surest guide to the presence and degree of mitral incompetence Fortunately from the nature of things we are able in a matter of days to check our clinical diagnoses against objective proof—the surgeon s forefinger in the atrium is a fairly sensitive guide to the presence of a regurgitant stream Fig 11 shows how our clinical assessment stood up to surgical exploration It will be seen that in 61 per cent of our cases clinical and surgical findings tallied and in 25 per cent more they were in reasonable agreement but in 14 per cent the clinical diagnosis was more or less seriously wrong Such clinical errors have been reported in other series (Baker *et al* 1952 Venner and Holling 1953, etc)

In detail there were 5 cases in whom a systolic murmur was thought to be evidence of a minor regurgitation which at operation were found to have been pure mitral stenosis For the rest all errors were on the side of underestimating the degree of mitral incompetence —at least as judged by palpation

One notes however that all but one of the operated patients had severe or significant stenosis and that in very few has the post operative follow up failed to show significant improvement from the relief of stenosis Such results are against gross mitral incompetence

Again analysis of the operative findings (Table I) shows that moderate or marked mitral incompetence was recorded in 6 patients

with tight stenosis and 7 with fairly marked stenosis In the former at least one doubts if the palpable regurgitant jet was of serious hæmo dynamic importance

The anatomy of the mitral valve is now receiving detailed attention (Brock 1952) and it would appear that regurgitation with tight or marked stenosis depends on three main factors the state of the anterior cusp the rigidity of the orifice and the axis of the orifice whether central or directed posteriorly A patent orifice directed toward the inflow tract of the right ventricle is less likely to allow significant regurgitation than a similar or smaller hole facing the main ventricular outflow stream (Harken *et al* 1952) Table II shows our results reviewed in the light of those anatomical considerations

TABLE I

Degree of Stenosis and Incompetence

50 Operated Cases

TIGHT M S 1×0 5 cm or less		39
Degree of Mitral Incompetence		
None	28	
Slight	5	
Moderate	4	
Marked	2	
MODERATE M S >1×0 5 <2×1 cm		9
Degree of Mitral Incompetence		
None	2	
Moderate	3	
Marked	4	

TABLE II

Tight Mitral Stenosis <1×0 5 cm

MODERATE MITRAL INCOMPETENCE		4
Anterior cusp short in	3	
Buttonhole in	1	
MARKED MITRAL INCOMPETENCE		2
Central orifice in	1	
Gaping orifice in	1	

Division of the commissures may allow of improved closure even with relatively heavy sclerotic valve curtains but a shortened immobile anterior cusp remains a most depressing finding at operation

RHEUMATIC ACTIVITY —My colleague will have something to say of the pericardial and pleural reactions observed at operation Previous series (*e g* Entrickap 1953) have revealed a surprisingly high incidence of Aschoff nodes in biopsy specimens of the left auricular appendage amputated at operation Our experience has been similar—positive biopsies in 13 of 41 cases reported to date *i e* in about one third From the chart (Fig 12) it is apparent that in our series there was no tendency for positive results to be associated with the younger patients if

anything the average age is higher in the positive than in the negative groups The relation of such Aschoff bodies to active rheumatic infection in middle aged patients with no clinical evidence of active carditis has been questioned, but the validity of left auricular biopsy as a guide to the state of the heart muscle seems well established (McKeown, 1953), It is of interest too that 2 patients have developed active rheumatism in the post operative period one with generalised joint pains and one with pericarditis this is in accord also with general experience (Annotation, *Lancet* 1953 Logan and Turner 1953, Soloff *et al*, 1953)

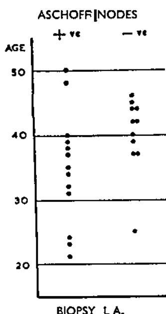


Fig 12 —Biopsy findings in left atrium correlated with the ages of the patients

These findings call in question our whole conception of cardiac rheumatism and *suggest that smouldering infection persists* for decades in a proportion of individuals

Assessment of Results —It is too early to give a reasoned statistical assessment based on adequate post operative follow up Few of the cases have been followed for more than a year many for only a few months or weeks A summary of the results will be given by Professor Douglas It is apparent however that the immediate results in our series as in others are astonishingly good

One may quote the two women in advanced pregnancy both the subjects of desperate attacks of pulmonary congestion and hæmoptysis who after operation proceeded uneventfully to full term and had normal spontaneous trouble free deliveries the iron moulder disabled for seven years who within a month rode a bicycle from Dundee to Perth and back (40 miles) and is now earning over £10 a week in a factory the grocer unable to walk more than 50 yards and in and out of hospital repeatedly in failure who now does a full day s work and walks 4 5 miles for pleasure the bus conductor seized when fishing with acute pulmonary congestion sitting hunched against the wall of a hut all night in great agony of mind and physical distress who now is able to walk 5 miles on a rough shoot without ill effect the housewife long disabled who boasted with evident glee that she had washed her blankets or the young woman who until the fifth month of her pregnancy had worked four hours a day cleaning a cinema in addition to her own family and domestic chores Many of them obviously are doing too much but such is their delight at new found freedom that dissuasion is difficult I know of no comparable benefits from any drug—and from a physician that is at once a confession and a tribute

PART II

SURGICAL CONSIDERATIONS

Here in Edinburgh where your experience with the operation is so much greater than ours it would be pretentious to formulate opinions about the general problems involved and so I propose to stick to matters of fact—to describe as accurately as I can what we did and what we found

OPERATIVE TECHNIQUE —Anæsthesia was induced with a small dose of pentothal and tubarine (30 mg) and maintained with intra tracheal gas oxygen One per cent procaine hydrochloride was given intravenously as a continuous drip infusion throughout the operation As a rule about 200 ml of the solution was administered containing 2 gm of procaine Blood was kept at hand but was only given in exceptional cases

The operative approach was through the bed of the sixth rib which was exposed by an antero lateral submammary incision The auricle was inspected for contractility and in its absence great care was taken in the initial handling to avoid dislodging clot It was opened near its tip and allowed to bleed freely A mitral clamp was then applied and the opening enlarged to admit the forefinger

The anterior of the atrium was then carefully explored to determine the nature of the valve lesion When this had been done as accurately as possible the valvotomy was begun by engaging the orifice in the finger tip and thrusting the finger through as far as possible As a rule one or both commissures split as the result of this manœuvre In this case further splitting was achieved by using the edge of the forefinger nail Finally the finger was again advanced into the ventricle and the chordæ tendineæ below the valve orifice separated in an attempt to minimise obstruction from this cause

In patients who had had systemic emboli the auricle was excised flush with the atrium but in others only the tip was removed Fine interrupted sutures of black silk were used to close the auricular incision

After closure of the chest water seal drainage was instituted and continued for forty eight hours The patient got out of bed as a rule about the eighth post-operative day and was discharged in about fourteen days

What we found at operation and after may be discussed under the headings the surgical pathology the technical difficulties the operative hazards and the results

SURGICAL PATHOLOGY —The pathological lesions of mitral disease found at operation seem to be restricted to three principal sites the lungs the auricle and the valve itself

(1) *The Lungs* —In a high proportion of cases there was evidence at operation of previous or intercurrent pulmonary disease (Table III) For example in one third of the cases there were pleural adhesions

often extensive sometimes obliterating the pleural cavity entirely and firmly binding the lung down to the pericardium In nine cases (15 per cent) there was recent creamy exudate on the surface of the lung which could be wiped off with gauze I take it that this represented a resolving pleurisy and was an earlier stage of the previous lesion Taking these two groups of cases together, almost half the cases therefore had evidence of old or recent pleurisy The pulmonary lesion underlying the pleurisy was presumably infarction of the lung

In six cases (10 per cent) a pleural effusion of some size was present and in three of these it was quite large—over a pint

An unusual pulmonary lesion met with was the presence of large sub pleural blebs of fluid in the free edge of the lung This might have been thought to have been evidence of pulmonary œdema but there was no pre operative clinical evidence of this

TABLE III

The Surgical Pathology of Mitral Disease

Lesion	Number of Cases	Per Cent
Pleural adhesions	23	35
Pleural exudate	9	15
Pleural effusion	6	9
Auricular contracture	18	28
Auricular thrombosis	13	20

(2) *The Auricle*—In eighteen cases (28 per cent) the auricle was shrunken and fibrosed and in thirteen of these there was thrombus within it Often the thrombus was well organised and white and required a good deal of sharp di section before the actual cavity could be entered but not infrequently on the inner aspect of the organised thrombus recent thrombus was present which was washed out when bleeding occurred The auricular shrinkage may presumably be due to rheumatic carditis or to thrombosis In nearly all cases fibrillation was present and so possibly contraction of an organising thrombus is principally concerned

Calcification of the auricle was met with on two occasions on one occasion extending down along the atrial wall and making the atrium into a rigid cavity

(3) *The Valve*—In describing the pathology of the valve one is handicapped by the fact that reliance has to be placed upon tactile impressions perceived through a rubber glove If the experiment is tried of handling a shilling with the bare and with a gloved hand one is forcibly struck with the loss of fine discrimination in the latter For example it is difficult even to be sure that the edge of the coin is milled

This is of particular importance in assessing the volume and force of a regurgitant jet of blood in mitral incompetence and I feel sure that the inability of the surgeon s finger to feel one by no means implies that a leak may not be present

However even with the handicap of trying to form a visual impression from such imperfect tactile impulses it is quite evident that the normal filmy cusps of the mitral valve restrained from inversion by the tenuous chrodæ tendineæ are distorted out of all recognition in the majority of cases (Fig 13) In their place is substituted a shallow cone of thickened tissue in whose apex there is a small aperture to which are adherent hard scarred remnants of the chordæ and papillary muscles The larger anterior cusp may or may not maintain some degree of its original mobility depending upon whether fibrous contraction has been a feature If it does then incompetence of the valve is exceptional though in one case this was seen One supposes that the posteriorly placed valve orifice is occluded by the bulging valve cusp above it When it does not and the anterior cusp is shortened and fibrosed the orifice is pulled more centrally towards the atrio ventricular septum and a large regurgitant gush of blood occurs with each ventricular systole

ORIFICE —We have usually found the orifice to be surrounded by puckered and indurated scar tissue often calcified with free calcium readily palpable in the atrial cavity It is a matter of great interest that calcification in this rheumatic process should be so common whereas in other rheumatic processes in pericardium joints and tendons it is comparatively rare

The shape of the orifice has usually been ovoid and has varied in size from being impalpable to 2 5 cm In the latter case regurgitation has always been severe The case in which the valve orifice was impalpable was a woman of 50 years She had been breathless on exertion for many years and this symptom had become much worse during the last two years A cerebral embolus had occurred in May 1951 with a temporary hemiplegia and aphasia During the last six months before admission she had been able to get about on the level but had become very distressed on inclines or stairs During the valvotomy the whole margin of the original orifice was carefully palpated with the forefinger but no opening admitting even part of the tip of a finger could be palpated and a linear indurated fissure was all that could be felt By using a great deal of force this was eventually split It gave way so suddenly that the finger came against the anterior ventricular wall with great force and ruptured it fortunately thanks to aortic transfusion not with fatal results

In this series the anterior cusp could be said to be mobile in about half the cases to be rigid and immobile in one third and in the remaining sixth to be intermediate between the two Below the valve the chordæ could often be felt matted and fixed together so as to constitute in some cases a sub valvular stenosis

It is worth emphasising that even in the most mobile cases the valve cusps were grossly abnormal and in no way resembled the flaps of the healthy mitral valve On the whole one s impression has been that of a shallow cone with a terminal aperture as a rule less than

1 cm The walls of the cone may be mobile and soft in the case of pure stenosis or rigid and indurated in the case of incompetence but never has any sign of the open and shut action of the normal mitral valve been perceived

TECHNICAL DIFFICULTIES—The principal technical difficulties have been associated with (1) the state of the auricle and (2) the state of the valve margins

(1) *The Auricle*—A small fibrotic shrunken auricle filled with organised thrombus constitutes a technical difficulty which at present is associated with an increased operative risk As the auricle itself is opened to introduce the finger there is a risk of dislodging recent thrombus with a resultant systemic embolus There is also a risk

FIG 13—Photograph of the atrio ventricular valves of a patient with mitral disease dying without operation On the left the mitral on the right the tricuspid The atria have been excised and the superior aspect of the valves is seen The mitral valve is the site of severe stenosis Note the thickened and indurated edge of the typical ovoid orifice which measures less than one centimetre

FIG 14—Photograph of atrio ventricular valves in two patients dying after mitral valvotomy The size of the mitral orifice achieved by the valvotomy is seen Though in each case it is 2 cm in its transverse axis it is still far from the normal size

FIG 15—Photograph of atrio ventricular valves in a patient dying three weeks after mitral valvotomy The cause of death was the development of an infected thrombus at the medial commissure It can be seen to have grown until it has almost completely occluded the orifice

of major hæmorrhage which cannot be readily controlled because of tearing of the shrunken auricle As the finger is advanced into the atrium a shrunken auricle often splits in a vertical direction in addition to the horizontal incision already made and this split may pass down on the medial side of the atrial wall and require great ingenuity in closure As long as the wall of the auricle itself is tough it is usually possible by the insertion of repeated interrupted sutures and finger pressure to close the tear But if the muscle is friable by reason of recent myocarditis the stitches may tear out as fast as they are inserted and we have lost one patient from this cause If the right ventricle is grossly hypertrophied the heart may be rotated so that the auricle is very posteriorly placed in the pericardium and this together with a small shrunken auricle constitutes a real operative difficulty

(2) *Valve Orifice*—The splitting of the valve commissures with the forefinger may be very easily achieved if the edges of the orifice are soft and pliable However if induration and calcification is present there is a very serious problem I personally, have had little success with the use of the valvotome and except on a few occasions it has failed to divide calcified and indurated commissures much more than I have achieved with the finger nail The maximum amount of splitting of the commissure occurs when the finger is first thrust through the valve up to the proximal interphalangeal joint and the further aperture



Fig 13



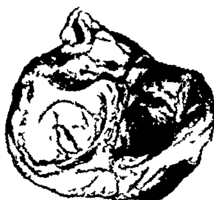


Fig 14



Fi 15

attained thereafter is often small In splitting the lateral commissure gentle counter pressure on the wall of the ventricle has been found helpful It is obviously of great importance to record the extent and adequacy of the valvotomy and estimated measurement though imperfect seems the most accurate method available After the splitting of the valve margins has been achieved a fairly accurate concept of the width of the new orifice may be obtained by passing the tip of the forefinger from one commissure to the other In this series the terminal aperture has usually measured 2 to 2 5 cm But I must confess to have been disappointed at post mortem to see how small this orifice really is (Fig 14)

Finally in discussing the technical aspects of the valvotomy I feel strongly that we should not leave our practitioner colleagues under the impression that the valve has been returned to anything like its original state and the best description in my own mind of what is achieved by operation in the favourable cases in this series is that a shallow cone with an aperture of 1 cm at its tip is converted into one with an aperture of 2 2 5 cm This doubling in aperture size seems to account for the dramatic improvement which some of these patients show

THE HAZARDS OF OPERATION —Many patients show profuse sputum post operatively sometimes blood stained often when pre operatively the chest has been judged to be clear radiographically and by auscultation Occasionally this sputum is so profuse as to make one feel that it must be due to pulmonary œdema But it is difficult to understand why pulmonary œdema should occur in a patient who is at rest in bed and in whom the mitral aperture has been enlarged It may perhaps be due to a diminution in pulmonary vasomotor tone allowing the transmission of a high pulmonary artery pressure directly to the capillaries though this is mere conjecture

Clinical signs of pulmonary emboli *i e* chest pain and hæmoptysis have been relatively common in this series As a rule there has been no sign of deep venous thrombosis in the legs and one has been driven to the conclusion that the source of the embolus has been the right auricle A number of patients have shown pyrexia lasting for some time—one case for as long as a month post operatively without any definite physical signs to account for it This has been ascribed to a recrudescence of a rheumatic infection and it has certainly often been associated with a high E S R Post operative pleural effusion has been a relatively constant feature

FATAL CASES (Table IV) —There have been five deaths in the series In the first only an exploratory thoracotomy was carried out Because of extreme shrinkage of the auricle and extensive calcification of the atrial wall it was found impossible to proceed with the intra cardiac part of the operation She developed myocardial failure and died forty eight hours later with pulmonary œdema

The second a man of 34 developed repeated rigors and died

three weeks after operation At post mortem there was present at his valvotomy site infected thrombus from which a pure culture of pneumococcus was grown (Fig 15) This must have been a re crudescence of a latent bacterial endocarditis It was striking that life was possible with the minute orifice which is visible on the illustra tion and measured about 3 mm

TABLE IV

Deaths after Mitral Valvotomy

S n N	Ag	Day Post-oper t e	P M F d g
6	48	3	Pulmonary œdema
11	34	28	Infected valve thrombus
13	38	33	Superior venocaval thrombosis
57	41	3	Atelectasis of lungs
58	44		Tear of auricle

The third patient died six weeks after operation from thrombosis of the superior vena cava Its nature and origin is unexplained She had repeated pulmonary emboli and at post mortem both lungs were the site of extensive infarcts

The fourth patient was a man of 41 who died on the third post operative day suddenly during a fit of coughing His progress up

TABLE V

Results of Valvotomy in Mitral Disease followed over Six Months

The figures in brackets are percentages

Les	N mb	Good	F	U mp oved
M S	3	18 (78)	3 (13)	2 (9)
M S+M I	10	5 (50)	3 (30)	2 (20)
Whole group	33	23 (70)	6 (18)	4 (12)

to that time had been reasonably satisfactory though his operation had been technically difficult because of a very calcified valve At autopsy he was found to have extensive atelectasis of both lungs and an inhalation of vomitus into his right lung There was no sign of pulmonary embolus or a coronary occlusion His death I think was due to acute anoxia and was preventable

The fifth death was the one already referred to in which the shrunken auricular wall was so friable that the stitches tore out as fast as they were inserted He had sub acute pericarditis with bread and butter heart

RESULTS (Table V)—Of the 64 cases 33 have been followed for six months and 18 for over a year

The results closely resemble those reported by Baker *et al* (1952) Turner and Logan (1953) and Holmes Sellors *et al* (1953) Taking

the group as a whole 70 per cent of the cases derived significant benefit As would be expected the result in the stenotics was better than that in those with incompetence about 80 per cent as compared with 50 per cent having good results I must confess to being perplexed at the improvement in the patients with regurgitation and to wonder how often it is due to psychological effects—the patients have had their operation and feel that things must be better—as it were they develop a vested interest in the result

Whatever may be the explanation it will be very difficult to assess the results of any operation specifically designed to correct regurgitation since simple valvotomy gives good results in half the cases

From the surgical viewpoint and from the behaviour of inflammatory strictures in other viscera one would suppose that a considerable proportion of these patients will show temporary relief only perhaps for some years and that thereafter a gradual recurrence of the symptoms will appear However if even five years of comfort in the miserable existence of a patient with mitral stenosis are achieved the operation will have been well worth while

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CHEMOTHERAPY IN PULMONARY TUBERCULOSIS

By JOHN CROFTON

From the Department of Tuberculosis and Diseases of the Respiratory System University of Edinburgh

THE mortality figures for respiratory tuberculosis over the last fifty years show that up to the beginning of the recent war, there was a steadily downward trend interrupted only by the First World War (Fig 1) It is generally agreed that this downward trend is mainly

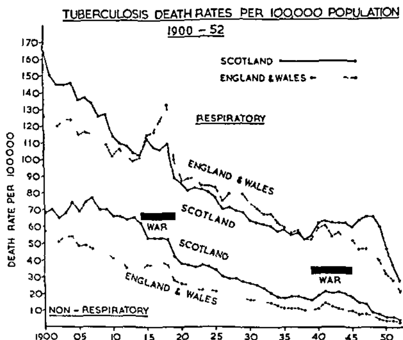


FIG 1

to be attributed to the improvement in social conditions The introduction of sanatorium treatment over the first decade or so of the century the widespread use of artificial pneumothorax during the 1920s the popularity of thoracoplasty during the 1930s seem to have had no sudden or dramatic effect on the mortality of the disease however effective these treatments may have been in individual cases During the recent war there was a rise in mortality particularly from respiratory tuberculosis both in Scotland and in England and Wales although the upward trend ceased in England and Wales after 1941 In Scotland as is notorious the mortality continued to rise after the

Read 1 th November 1953

end of the war Streptomycin first became widely used in 1948 49 and immediately there was a very rapid decrease in the mortality rate The decrease was the more impressive in Scotland as the rate had been rising up to this time The decrease in mortality is particularly dramatic among the younger age groups which tend to suffer from the acute exudative disease which is particularly susceptible to chemo therapy Fig 2 shows the trend of mortality rates in males and

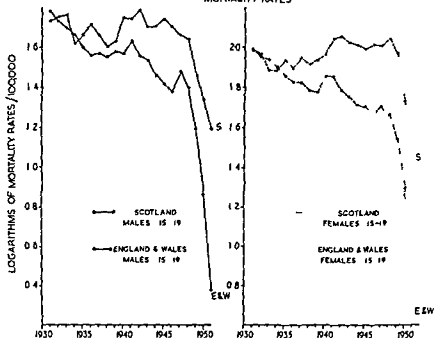


Fig —(By courtesy of Dr Lilli Stein of the Department of Public Health and Social Medicine University of Edinburgh)

females aged 15 19 in England and Wales and in Scotland The astonishing decrease in the mortality rate since the introduction of streptomycin is seen in both sexes From these figures one can surmise that treatment is having an effect on the disease not only in individual cases but on a national scale

It is impossible to cover very much of the enormous subject of chemotherapy of tuberculosis in an hour s lecture This afternoon I intend briefly to review the results of chemotherapy as revealed in some of the Medical Research Council trials and to give a rather fuller review of the literature regarding the influence of combined therapy in preventing the emergence of drug resistance to tubercle bacilli Finally I shall try to give some assessment of the present situation from the point of view of the practical physician

DRUGS AVAILABLE FOR THE CHEMOTHERAPY OF TUBERCULOSIS

These may be listed as follows —

Established Drugs —(1) Streptomycin (2) Salts of para amino salicylic acid (3) Isoniazid

Possible Accessory Drugs —(1) Thiosemicarbazones (2) Terramycin (3) Viomycin

The possible accessory drugs listed above are those which may be of some value in preventing the emergence of resistance to the established drugs though probably in themselves not being important therapeutic agents

RESULTS OF CHEMOTHERAPY

In this review I propose only to cover the results of chemotherapy in acute tuberculous bronchopneumonia in various Medical Research Council trials since 1948 using radiographic change as the main criterion In Fig 3 are shown the proportions of patients in whom there was moderate or considerable radiographic improvement after six months observation or who remained unchanged deteriorated or died These were all controlled trials each trial consisting of at least 2 treatment groups allotted at random The first results are those of the control group treated on bed rest only during the first trial of streptomycin It will be seen that 27 per cent died and that another 34 per cent deteriorated during the six months period As far as deterioration or death was concerned the results with all the other drugs or drug combinations shown in this figure are very much better than in those treated with bed rest alone The highest mortality listed was 8 per cent of 109 patients treated with daily streptomycin alone Only 16 per cent of the patients in this group deteriorated Most of those deteriorating or dying will have been patients in whom streptomycin resistant organisms emerged It will be seen that all the groups given chemotherapy showed very many more patients with radiographic improvement than among the controls treated with bed rest alone The proportions showing considerable improvement are very similar in all the groups in which streptomycin was included When P A S was used alone the proportion showing considerable improvement is distinctly lower than in the other chemotherapeutic groups but markedly higher than in those on bed rest alone Fig 4 is derived from later Medical Research trials (M R C 1952*a* M R C 1953*a* and M R C 1953*b*) The cases treated are similar to those in Fig 3 with the exception that in some cases the disease was unilateral and the criteria of age were less limited all the patients shown in Fig 3 were aged 15 to 30 but those in this figure might be of any age the assessments in this figure were made at three months instead of six months as in Fig 3 The group treated with 1 g streptomycin daily combined with P A S (sodium) 5 g four times a day is common to Figs 3 and 4 and forms the basis of comparison with the other treatments It will

be seen that, compared with this group among those treated on isoniazid alone not so many showed radiographic improvement of a high degree and there were some cases of deterioration The latter were probably associated with the development of drug resistance

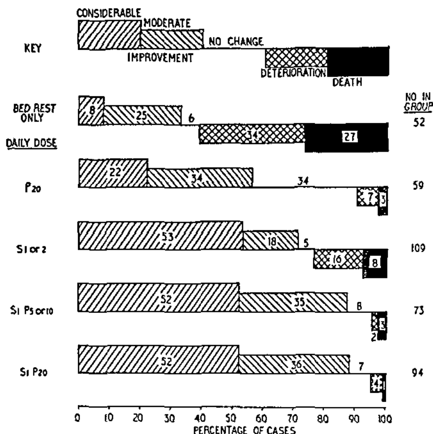


FIG 3—Radiographic change over six months in patients aged 15 30 with acute bilateral tuberculous bronchopneumonia treated by bed rest alone or with various forms of chemotherapy (continued for at least 3 months)

P20 = P A S (sodium) 20 g daily in 4 divided doses S1 or 2 = streptomycin 1 g or 2 g daily S1P5 or 10 = streptomycin 1 g daily combined with P A S (sodium) 5 or 10 g daily in 4 divided doses S1P 0 = streptomycin 1 g daily combined with P A S (sodium) 20 g daily in 4 divided doses Medi al Research Council trials figures derived from Daniels and Bradford Hill (195)

The results with streptomycin 1 g daily combined with isoniazid 100 mg twice a day were even better than those with streptomycin and P A S The evidence suggests that this combination is probably the most powerful available, although there are certain disadvantages which will be discussed later The final group includes those treated with P A S (sodium) 5 g four times a day and isoniazid 100 mg twice a day It will be seen that the radiographic improvement

although not quite as good as that with streptomycin and isoniazid in combination, is very similar to that with streptomycin and P A S and rather better than that with isoniazid alone

It is clear from this brief review that the results of treatment with any drug combination which includes streptomycin or isoniazid are very good and that there is little difference between the combinations

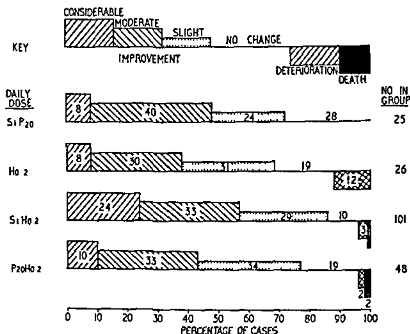


FIG 4—Radiographic change over three months in patients of any age with acute tuberculous bronchopneumonia unilateral or bilateral treated with various forms of chemotherapy

S1P20 = streptomycin 1 g daily combined with P A S (sodium) 20 g daily in 4 divided doses Ho 2 = isoniazid 200 mg daily in 2 divided doses S1Ho 2 = streptomycin 1 g daily combined with isoniazid 200 mg daily P oHo = P A S (sodium) 20 g daily combined with isoniazid 00 mg daily Figures from various Medical Research Council trials (195 a 1953a 1953b)

On the other hand P.A S alone is rather less effective These results of course are over comparatively short periods The effectiveness of any combination over long periods will depend on the proportion of patients in whom drug resistant tubercle bacilli emerge It is to this subject we must now turn

DRUG RESISTANCE

Where only one of the three main chemotherapeutic agents has been employed alone drug resistant organisms have emerged in 20 to 40 per cent of patients within three to four months (Figs 5 6

7, 8) Let us consider for a moment the possible significance of this resistance in the case of the three main chemotherapeutic agents

Significance of Streptomycin Resistance —When a patient s tubercle bacilli become streptomycin resistant on the routine test probably between 1 in 100 and 1 in 1000 of the population are actually resistant (Mitchison, 1950) Streptomycin may continue to have some effect on the remaining sensitive organisms for a further period which can probably be measured in weeks Thereafter it will have little effect

PREVENTION OF STREPTOMYCIN RESISTANCE BY P A S

NOTE RESISTANCE TESTS PERFORMED AFTER 3-4 MONTHS OF TREATMENT

KEY (FIGURES %)

AUTHORS	STREPTOMYCIN DOSE g	P A S DOSE g	NO OF CASES	STREPTOMYCIN RESISTANT	STREPTOMYCIN SENSITIVE	RESULTS UNKNOWN	SPUTUM NEGATIVE	
U S VETERANS ADMINISTRATION 1948	1g DAILY	NONE	655	30	16	19	35	NO P A S.
DANIELS & BRADFORD HILL 1952	1g DAILY	NONE	109	29	14	42	15	NO P A S.
TEMPEL 1952	1g DAILY	NONE	37	43	22		35	NO P A S.
MEDICAL RESEARCH COUNCIL 1952	1g DAILY	5g DAILY	34	24	25	13	38	SODIUM P A S. 5 20g DAILY STREPTOMYCIN DAILY
MEDICAL RESEARCH COUNCIL 1952	1g DAILY	10g DAILY	39	25	24	8	43	
FRIEDMAN et al 1952	1g DAILY	14g DAILY	50	8	44		48	
DYE 1952 (U S VETERANS)	1g DAILY	16 5g DAILY	309	7	21		72	
DANIELS & BRADFORD HILL 1952	1g DAILY	20g DAILY	95	4	54	14	28	
MEDICAL RESEARCH COUNCIL 1955(a)	1g DAILY	20g DAILY	78	5	16	10	69	
DYE 1952 (U S VETERANS)	1g TWICE WEEKLY	16 5g DAILY	149	6	25		69	P A S DAILY STREPTOMYCIN TWICE WEEKLY
PITTS et al 1953	2g TWICE WEEKLY	16 5g DAILY	98		14		86	
TEMPEL 1952	2g TWICE WEEKLY	16 5g TWICE WEEKLY	103	9	21		70	P A S & STREPTOMYCIN TWICE WEEKLY

FIG 5 —Note that P A S doses are given in terms of P A S (sodium)

on the course of the disease Moreover if in such a patient strepto mycin is later used in combination with a second drug the streptomycin will no longer be effective in preventing resistance to that second drug In most cases once a patient s tubercle bacilli become resistant to streptomycin they remain so permanently although very occasionally reversion seems to occur Even more sinister these streptomycin resistant organisms may be handed on to a second patient and streptomycin is unlikely to be effective in that patient For instance a patient (reported in detail elsewhere) was infected probably by his wife with an organism which was found to have a streptomycin resistant ratio of 8 that is to say slightly streptomycin resistant The patient had

never had streptomycin and it was assumed that the organisms were sensitive when he was started on streptomycin 1 g daily combined with isoniazid 100 mg twice a day Within two months his organisms had become isoniazid resistant he was the only patient in our series from whom isoniazid resistant organisms were obtained on this combination of drugs

Significance of P A S Resistance—When P A S resistant organisms have emerged it should be assumed that the drug is no longer effective in that patient at least when the bulk of his organisms have become resistant to the drug although there is little direct evidence on this point We have shown that resistant organisms may persist at least in some patients for up to three years after the cessation of a course of P A S alone although it may be that in a proportion there is reversion to full P A S sensitivity The presence of such resistance abolishes the effect of P A S in preventing the development of resistance to a second drug (Turnbull and others 1953) We have now had several cases to be published elsewhere in which P A S resistant organisms have been handed on that is in which patients have been infected with P A S resistant organisms probably derived from a patient who had received the drug alone

Significance of Isoniazid Resistance—When a patient s tubercle bacilli become isoniazid resistant it is probable that the isoniazid is of little further value So far I know of no evidence about the effect of the emergence of isoniazid resistance in abolishing the preventive action of the drug on the emergence of resistance to a second drug There is some evidence that drug resistance is less permanent than in the case of streptomycin Certainly it is our experience that it is common for a patient s organisms to revert to a lower degree of isoniazid resistance after cessation of the drug There is some suggestion that highly isoniazid resistant organisms are less virulent (Barnett and others 1953) This does not apply to the lower degrees of isoniazid resistance and it is these possibly more virulent degrees of resistance which tend to remain So far I know of only one case where an isoniazid resistant organism was handed on to a second patient but this was a laboratory infection (Borgen 1953)

PREVENTION OF DRUG RESISTANCE BY COMBINED CHEMOTHERAPY

Prevention of Streptomycin Resistance by P A S—In Fig 5 is reviewed some of the evidence concerning the prevention of the emergence of streptomycin resistant tubercle bacilli by the use of P A S in various doses and combinations The P A S doses are given in terms of P A S (sodium) Some of the figures in this and subsequent tables have had to be calculated from data given by the author or even estimated from diagrams and so can only be regarded as approximate It will be seen that when streptomycin is given

daily the proportion of patients in whom streptomycin resistant organisms emerge decreases steadily with increase in dose The best results have been obtained when 5 g of P A S (sodium) is given four times a day Pitts *et al* (1953) obtained very good results employing daily P A S in doses equivalent to 16 5 g of sodium salt combined with *streptomycin twice weekly* These *very good results may be* partly because their patients were mostly young soldiers and it is to be noted that in 86 per cent there was sputum conversion The United States Veterans Administration (Dye 1952) obtained less dramatic results, the 6 per cent of patients in their series who developed

PREVENTION OF STREPTOMYCIN RESISTANCE BY ISONIAZID TERRAMYCIN THIOSEMICARBAZONES

NOTE RESISTANCE TESTS PERFORMED AFTER 3 4 MONTH OF TREATMENT

KEY (FIGURES %)

AUTHORS	STREPTOMYCIN DOSE g	SECOND DRUG	NO OF CASES	STREPTOMYCIN RESISTANT	STREPTOMYCIN SENSITIVE	RESULTS UNKNOWN	SPUTUM NEGATIVE	
U S VETERANS ADMINISTRATION 1948	1g DAILY	NONE	655	30	16	19	35	STREPTOMYCIN ALONE
DANIELS & BRADFORD HILL 1952	1g DAILY	NONE	109	29	14	42	15	
TEMPEL 1952	1g DAILY	NONE	37	43	22		35	
		ISONIAZID						
MEDICAL RESEARCH COUNCIL 1953 ( )	1g DAILY	200 mg DAILY	109	2	16	7	75	ISONIAZID (SECOND DRUG)
PITTS et al 1953	2g TWICE WEEKLY	150-300mg DAILY	99	2	9		89	
MEDICAL RESEARCH COUNCIL 1953(b)	1g TWICE WEEKLY	200 mg DAILY	94	3	20	1	76	
		TERRAMYCIN						
MILLER et al 1952	2g TWICE WEEKLY	5g DAILY	66		23		77	TERRAMYCIN (SECOND DRUG)
SCHWARTZ & MOYER 1952	1g TWICE WEEKLY	5g DAILY	9		56		44	
		THIOSEMICARBAZONE						
GREENBERG 1952	1g DAILY	100-200mg DAILY	55	13	5	24	58	THIOSEMICARBAZONES (SECOND DRUG)

FIG 6

streptomycin resistance being very similar to the proportion in another group treated by the same organisation with daily streptomycin as shown in Fig 5 The evidence therefore so far as it goes suggests that the use of streptomycin twice a week instead of daily has no advantages purely from the point of view of the emergence of strepto mycin resistant organisms over daily streptomycin When P A S was given twice weekly as well as streptomycin (Tempel 1952) strepto mycin resistant organisms emerged in a higher proportion (Fig 5) This is especially notable when it is remembered that these patients are similar to those in whom Pitts *et al* (1953) found no resistant organisms when treated with daily P A S and streptomycin twice a week

Prevention of Streptomycin Resistance by Other Drugs —In Fig 6 are shown some figures for the prevention of streptomycin resistance by isoniazid terramycin and thiosemicarbazones The incidence of

streptomycin resistant organisms is greatly reduced over three or four months by giving isoniazid whether streptomycin is administered daily or twice a week Terramycin in doses of 5 g a day is also effective when the streptomycin is given only twice a week The disadvantages are that terramycin in this dose given for so long is very expensive and that a number of patients are unable to tolerate it Lower doses are at present being investigated The evidence available suggests that thiosemicarbazones are not very valuable in preventing the emergence of streptomycin resistant bacilli I can find only one considerable series and it was uncontrolled Thiosemicarbazones have a high toxicity and are unlikely to be used for this purpose in future as other better tolerated drugs are now available

Prevention of P A S Resistance—Some data on the prevention of P A S resistance derived from various Medical Research Council trials, are presented in Fig 7 It will be seen that the combination of streptomycin with P A S has markedly reduced the incidence of P A S resistance, but that this reduction is more marked when P A S (sodium) is given in doses of 5 or 10 g a day than when it is given in doses of 20 g a day The evidence suggests however that isoniazid is even more effective than streptomycin in preventing the emergence of P A S resistance no resistant organisms have been recorded in a recent Medical Research Council publication (M R C 1953*b*)

Prevention of Isoniazid Resistance—In Fig 8 is given the incidence of isoniazid resistance when the drug is administered alone and also the reduction in its incidence when combined with streptomycin It will be observed that in the Medical Research Council series the incidence of isoniazid resistance is 3 per cent when streptomycin is given daily combined with 100 mg isoniazid twice a day, whereas when streptomycin is only given twice a week the incidence of isoniazid resistance is 9 per cent and resistant organisms form a high proportion of the sputa remaining positive Although these results are not at present confirmed by American studies (Pitts *et al* 1953 Dye *et al* 1953) the evidence is sufficient to suggest that the combination of streptomycin twice a week with isoniazid daily is an undesirable one to use unless further study proves its safety

The preliminary Medical Research Council report recently issued (M R C 1953*b*) indicates that P A S is highly effective in preventing the emergence of isoniazid resistant organisms even when given in doses of 5 g of sodium salt twice a day though the number of results is as yet small

EFFECTIVE DRUG COMBINATIONS

In view of the above results we can list the following drug combinations as being of probable practical use the advantages and disadvantages of each individual combination being indicated

(1) *P A S (Sodium) 5 g Four Times a Day Combined with Streptomycin 1 g Daily in a Single Injection*—This combination

has been found to be highly effective clinically Resistant organisms to either drug emerge in only a very small proportion of cases The disadvantages are that daily injections are necessary and that with daily streptomycin a proportion of patients higher in the older age groups suffer vestibular damage and become giddy A number of patients find this high dose of P A S causes unpleasant gastro intestinal effects

(2) *P A S (Sodium) 5 g Four Times a Day Combined with Streptomycin 1 g given Two or Three Times a Week*—This combination is clinically effective probably as effective or almost as effective as daily streptomycin combined with P A S The decreased frequency of the streptomycin injections is pleasanter for the patient and this decreased frequency much reduces the incidence of vestibular damage Streptomycin resistant organisms emerge in only a very small proportion of cases although the evidence is less definite in the case of P A S resistance The disadvantages are that injections are required even though less frequently and that the high P A S dosage causes gastro intestinal upsets in some patients

(3) *Streptomycin 1 g Daily Combined with Isoniazid* 100 *mg Twice a Day*—This is a highly effective combination probably the most effective of any at present available The incidence of both streptomycin and isoniazid resistance is very low The disadvantage is that daily streptomycin injections are required with the resulting discomfort to the patient and risk of vestibular damage In addition if the combination is unsuccessful and the patient s organisms become resistant to one of the two drugs by the time one discovers this after the two months delay in reporting the resistance tests the patient s organisms will probably have become resistant to the second drug and he will be deprived of the two most effective anti tuberculous agents

(4) *P A S (Sodium) 5 g Four Times a Day Combined with Isoniazid* 100 *mg Twice a Day*—This has been shown to be a very effective treatment possibly not quite as effective as daily streptomycin and isoniazid but much the same as streptomycin and P A S The great advantage is that it avoids the necessity of injections In addition the incidence of resistance to either drug is very low indeed Again the disadvantage of this combination is the toxicity of the high dose of P A S

(5) *P A S (Sodium) 5 g Twice a Day Combined with Isoniazid* 100 *mg Twice a Day*—Detailed evidence about the clinical effectiveness of this drug combination is not yet available Although the preliminary reports suggest that the incidence of drug resistance will be low the figures are at present small and it is not recommended that this combination should be generally used until more information is published If it fulfils its early promise then it will be a very valuable treatment as most patients can tolerate 10 g of P A S (sodium) a day and of course isoniazid in the doses used has virtually no toxicity

PREVENTION OF PAS RESISTANCE BY STREPTOMYCIN AND ISONIAZID

AUTHORS	NO OF CASES	PAS RESISTANT	PAS SENSITIVE	RESULTS UNKNOWN	SPUTUM NEGATIVE	KEY (FIGURES %)
MEDICAL RESEARCH COUNCIL (1950)	59	20	42	31	7	NO SECOND DRUG
MEDICAL RESEARCH COUNCIL (1950)	53	4	53	15	28	SM 1g DAILY Na PAS 20g DAILY
MEDICAL RESEARCH COUNCIL (1952)	42	5	66		29	
MEDICAL RESEARCH COUNCIL (1952)	72		77		23	SM 1g DAILY Na PAS 5 or 10g DAILY
MEDICAL RESEARCH COUNCIL (1953 b)	67		24	4	72	INAH 200 mg DAILY Na PAS 20g DAILY
MEDICAL RESEARCH COUNCIL (1953 b)	65		17	8	75	INAH 200 mg DAILY Na PAS 10g DAILY

FIG 7—SM = streptomycin Na PAS = PAS (sodium) INAH = isoniazid

PREVENTION OF ISONIAZID RESISTANCE BY STREPTOMYCIN OR PAS

NOTE

RESISTANCE TESTS PERFORMED AFTER 3-4 MONTHS OF TREATMENT

AUTHORS	STREPTOMYCIN DOSE g	ISONIAZID DOSE mg	NO OF CASES	ISONIAZID RESISTANT	ISONIAZID SENSITIVE	RESULTS UNKNOWN	SPUTUM NEGATIVE	KEY (FIGURES %)
MEDICAL RESEARCH COUNCIL 1953 (a)	NONE	200 mg DAILY	93	3	22	4	39	NO STREPTOMYCIN
DYE et al 1953	NONE	150 mg DAILY	36	22	11	17	50	NO STREPTOMYCIN
MEDICAL RESEARCH COUNCIL 1953 (a)	1g DAILY	200 mg DAILY	109	3	8	4	85	STREPTOMYCIN
PITTS et al 1953	2g TWICE WEEKLY	150-200mg DAILY	98	3	8		89	STREPTOMYCIN
DYE et al 1953	2g TWICE WEEKLY	150 mg DAILY	36		3		97	STREPTOMYCIN
MEDICAL RESEARCH COUNCIL 1953 (b)	1g TWICE WEEKLY	200mg DAILY	94	9	14	3	74	STREPTOMYCIN

AUTHORS	PAS DOSE g	ISONIAZID DOSE mg	NO OF CASES	ISONIAZID RESISTANT	ISONIAZID SENSITIVE	RESULTS UNKNOWN	SPUTUM NEGATIVE	KEY (FIGURES %)
MEDICAL RESEARCH COUNCIL 1953(b)	20g DAILY	200mg DAILY	67		27	1	72	PAS (SODIUM)
MEDICAL RESEARCH COUNCIL 1953(b)	10g DAILY	200mg DAILY	65	2	23		75	PAS (SODIUM)

FIG 8

Clinical Application of Various Drug Combinations

When chemotherapy seems likely to be the definitive treatment in a case of pulmonary tuberculosis that is in uncomplicated cases with only minimal or no cavitation, then the combination of daily streptomycin with daily isoniazid is justifiable in that this is the most effective treatment known But, as daily streptomycin injections may not be easy to arrange in the home this recommendation may apply mainly to patients in hospital and because of the risk of vestibular damage, to younger patients who are less liable to suffer from vestibular toxicity If the patient is to be treated at home or if he is in the age group where vestibular toxicity is a higher risk then it is probably better to employ the well established treatment of streptomycin 1 g three times a week combined with P A S (sodium) 5 g four times a day But there is now an alternative 20 g of P A S (sodium) daily combined with isoniazid 100 mg twice a day This is a particularly useful combination if the patient is to be treated at home, as no injections are involved However it must be strongly impressed on the patient and on his private doctor that the full doses of both drugs should be taken Indeed, with the patient on bed rest at home there is something to be said for the visit of a nurse two or three times a week to give an injection the patient feels that he is in continuous contact with the service and this will encourage him to carry out the instructions It is possible that 10 g of P A S (sodium) daily combined with isoniazid may later replace the combination in which the daily dose of P A S (sodium) is 20 g but at present this is not to be recommended for reasons already given

When the case is a more complex one and when there are one or more large cavities and surgery is likely to be ultimately necessary, then it is wiser to reserve isoniazid and to treat the patient initially with streptomycin and P A S If he is acutely ill then one may start by giving daily streptomycin but after the acute phase is past streptomycin is dropped to 1 g three times a week continuing the P A S daily This leaves isoniazid available if the treatment fails to prevent the emergence of drug resistance It may be that in the future especially if the patient is being treated at home the initial treatment in such a case may be daily isoniazid and daily P A S keeping streptomycin and terramycin in reserve in case the first combination fails to prevent the emergence of resistance

If there is a history of any of the three main drugs having been given alone then it is better to give the other two drugs If there seems to be any possibility that the patient s organisms may be resistant to two drugs as when there has been a history of P A S having been given alone in the first place followed by streptomycin and P A S together then it is wiser to give all three drugs until the result of the sensitivity tests is known

Duration of Chemotherapy

There are no firm data on which to base any definite statements about the optimum duration of chemotherapy in different cases This could only be based on a comparison of relapse rates with different durations of chemotherapy in the same type of case The use of longer and longer periods of chemotherapy is designed to minimise the chances of later relapse and most of us are steadily increasing the periods for which we give treatment A rough rule might be as follows —

Chemotherapy should be continued until (1) the patient has been free from significant symptoms for at least three months (2) the temperature has been normal for at least three months (3) the erythrocyte sedimentation rate has been normal for at least three months (4) the sputa or laryngeal swabs have been negative on culture for at least six months (5) if cavities were present and no collapse therapy or surgery is being employed until all cavities have been completely closed on the radiograph for at least six months All these criteria where relevant must be fulfilled that is to say for each patient the criterion which involves the longest period of treatment must be selected

Conclusion

Pulmonary tuberculosis is notoriously a relapsing disease Present experience suggests that the relapse rate may be substantially reduced by modern treatment with prolonged chemotherapy often followed by surgery But we should not be satisfied until there are no relapses We should also ask ourselves why we should have to be discussing the treatment of pulmonary tuberculosis at all King Edward VII said of this disease If preventable why not prevented? It is a grave slur on the capacity of our society that this preventable disease continues to flourish forty years later It is up to all of us doctors and laymen alike to remedy a discreditable situation

Summary

(1) Streptomycin salts of para aminosalicylic acid and isoniazid are well established in the treatment of pulmonary tuberculosis

(2) A review of six years of Medical Research Council trials of chemotherapy in bronchopneumonic tuberculosis emphasises the revolution which has occurred In the first phase of the trials 27 per cent of the patients treated on bed rest alone over six months died and over 60 per cent either died or deteriorated When patients with the same type of disease were treated with streptomycin 1 g daily combined with P A S (sodium) 5 g four times a day approximately 90 per cent showed radiographic improvement and only about 5 per cent deteriorated or died over the same period Any chemotherapeutic combination which contains either streptomycin or isoniazid is likely

to give very satisfactory results, although the combination of daily streptomycin and daily isoniazid is probably slightly more effective than any other

(3) It is concluded that drug resistance to either of the three main drugs is of clinical significance This is well established in the case of streptomycin and P A S and probable in the case of isoniazid

(4) The literature on the prevention of drug resistance by the combination of more than one drug is reviewed It is concluded that for the prevention of streptomycin resistance P A S should be given in the highest tolerated dose preferably the equivalent of 20 g of the sodium salt a day It makes little difference whether streptomycin is given daily or twice a week Daily isoniazid is also highly effective in preventing the emergence of streptomycin resistant organisms and terramycin in high doses also appears to be satisfactory The emergence of P A S resistance is prevented by combination with streptomycin or with isoniazid Isoniazid resistance is largely prevented by daily streptomycin but less effectively by streptomycin twice a week, daily P A S in doses of 5 g of the sodium salt four times a day is very effective and it seems possible that doses of 5 g twice a day may prove to be as good

(5) The advantages and disadvantages of different drug com binations are reviewed as are the indications for particular combinations in different types of case The proper duration of chemotherapy for particular cases is briefly discussed

In so far as results of investigations in this Department are referred to it should be made clear that these are the work of a group Dr A T Wallace and Miss Sheila Stewart carried out the bacteriology Dr F W A Turnbull co ordinated the work and was responsible for most of the clinical reviews Many of the patients were under the care of Drs N W Horne J D Ross and I W B Grant who contributed also much encouragement and many ideas Our Registrars House Physicians nursing staff and technicians gave us unfailing help The work has been supported by generous grants from the Royal Victoria Hospital Tuberculosis Trust I am most grateful to Mr C Shepley and Miss Brown of the Department of Medical Illustration for the trouble they have taken over the diagrams and to Mr T C Dodds for the reproductions

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ADDENDUM

The chemotherapy of tuberculosis has advanced since this lecture was given The most important amendments are as follows (1) Further investigation has confirmed the mutual prevention of drug resistance when isoniazid 100 mg and sodium P A S 5 g are given together twice a day (Medical Research Council 1955 *Brit Med Journ* 1 435) ( ) Isoniazid resistance can be substantially delayed or prevented by giving oxytetracycline (terramycin) 1 25 g four times daily with isoniazid 100 mg twice daily this is very expensive and should only be used in patients whose tubercle bacilli are resistant to streptomycin and P A S (Stewart *et al* 1954 *Brit Med Journ* 2 1508) (3) P A S resistance and subsequently streptomycin resistance may emerge in a small but important proportion of patient treated with streptomycin 1 g twice or thrice weekly together with daily P A S (experience of Edinburgh group to be published) (4) Durations of chemotherapy continue to increase nine months is now a minimum period and normally treatment would be given for nine to twelve months after the sputum becomes negative or a cavity closes

THE HAZARDS OF MAJOR SURGERY

By JOHN BRUCE C B E T D F R C S Ed

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ONE of the most inspiring and most reassuring trends of contemporary surgical practice has been the steady fall in the number of deaths following operation The achievement which this represents has been due less to improvements in surgical technique than to advances in related fields—to developments in anæsthesia, to a fuller knowledge of the physiology of ' shock and its prevention and management to a more adequate appreciation of the principles of fluid and electrolyte balance and to the introduction of the antibiotic drugs In the main the contribution of the surgical craftsman has been to exploit, with measurable success the discoveries of the physiologist and the pharmacologist He has applied his surgical techniques to the management of diseases formerly irremediable, such as portal hypertension and mitral stenosis and to organs like the pancreas and the adrenal gland which were formerly forbidden territories and he has overtaken certain of the problems that beset the pre operative and post operative management of his patients

There is some danger however that the very brilliance of his achievement may induce the surgeon to become complacent, or un mindful of the hazards that still attend operative procedures and the habit of critical retrospect is one in which he might indulge more frequently than he does Regular stocktaking—a pause at suitable intervals to balance the debits and the credits—is a salutary and sometimes humiliating corrective to uninformed satisfaction it has the added virtue that it is only against the background of past experience—and experiences—that the problems of surgery yet unsolved can be declared and the pattern of future research and progress elaborated

Some five years ago Sir James Learmonth initiated the valuable practice of regular and frank reviews of the deaths occurring in the respective units of his Department a practice which has stimulated a careful and exhaustive analysis of the factors contributing to each fatality and especially to those that are a direct consequence of surgical intervention These surveys are instructive in a number of ways They permit a critical scrutiny of the clinical management of the patient in

Read 6th December 1951

the light of an accurate knowledge of the pathology both of the original and of any coincidental disease they lead to the pooling of knowledge and experience of the rarer conditions and the more unusual complications and they assuredly temper the traditional optimism of the surgeon which has so powerful an ally in a short and sometimes convenient professional memory

It may be claimed—on good grounds—that the death rate of surgery is not the only yardstick of its dangers for surgery has its morbidity as well as its mortality its anxieties and its near tragedies as well as its complete failures None the less its mortality is a useful measure of its overall success and it is from this premise that I have elected to start to-day

The substance of this contribution is an account with comments of the deaths which occurred in a group of general surgical wards over a period of five years My first intention was to confine the report to the fatalities following major operations only Minor " surgery is difficult to define however and the occurrence of no fewer than three fatal pulmonary emboli following operation for trivial conditions has prompted a somewhat wider review

Over the period of five years 6510 patients were admitted for treatment and the outcome proved fatal in 282 (4 3 per cent. of the total admissions) In nearly 80 per cent of them (225 cases) autopsy was carried out to determine the exact cause of death, but this examination was refused or not requested on 57 occasions Nevertheless in 35 of these patients, the diagnosis had been clearly established at operation and of the remaining few, in only two instances was the cause of death not clinically obvious

In the first an elderly woman was submitted to operation on account of severe obstructive dyspnœa from extreme displacement of the trachea by a grossly enlarged thyroid but there was also a massive enlargement of the liver Death without obvious cause followed uneventful removal of a goitre which, on histological examination proved to be sarcomatous It is possible though not proved that the hepatomegaly was also neoplastic

In the second case a young man died in profound peripheral circulatory failure some twenty eight hours after the closure of a duodenal ulcer which had been perforated for twelve hours before admission Pre-operative resuscitation had proved extremely difficult and was in fact incomplete and despite the most vigorous post operative measures the circulatory depression was uninfluenced It was particularly unfortunate that a post mortem examination was not permitted here for the degree of collapse its early onset and its persistence during the whole course of the illness suggested in the light of other experiences that death might have been due to adrenal failure

For the purpose of this study the fatalities have been classified into —(*a*) Deaths without operation (71) (*b*) Post operative fatalities (211)

Deaths Without Operation

Operative treatment was not undertaken in 71 of the fatal cases which are enumerated in the accompanying table (Table I)

TABLE I

Causes of Death in 71 Patients dying without Operation

Advanced malignant disease	23
Lethal trauma	16
Cardiovascular diseases	13
Complications of peptic ulcer	7
Ulcerative colitis	2
Gross infections	6
Cirrhosis of liver	2
Uræmia	2

In nearly three quarters of them death was due to inoperable malignant disease to lethal trauma or to advanced cardiovascular lesions and the average age of these patients was 75 80 and 79 years respectively

Only two of the other groups merit particular mention There were two deaths—both in young patients—as a result of *ulcerative colitis* which will be considered later along with a series of deaths following operation for this condition and seven fatalities were caused by complications of *peptic ulceration* In two death was the result of severe hæmatemesis the first was received *in extremis* and died within a few hours but the other an elderly man was not submitted to operation despite the recurrence of a massive hæmorrhage in hospital At that time—the beginning of the quinquennium—a sufficiently defined therapeutic strategy in the management of the bleeding peptic ulcer had not been agreed upon between physician and surgeon it is now our practice to advise operation in patients over 50 who have a second appreciable bleed after admission to hospital

The remaining patients died as a result of perforation of the ulcer All were admitted in advanced peripheral circulatory failure—four as a result of late diagnosis and the last as a result of delay in seeking treatment This woman had perforated in London and had insisted on travelling home only to be brought to hospital in a moribund condition In each of these cases resuscitation was impossible

The Post Operative Deaths

The number of in patient operations undertaken during the five-year period was 5152 and death occurred in 211 cases an operative mortality of 4 1 per cent

A scrutiny of the age of these post operative fatalities reveals that the majority (62 per cent) were in patients over 60 and no less than a third (37 per cent) over 70 years of age while nearly half (48 2 per cent) were the result of malignant disease

These facts must to some extent mitigate our disappointment The lengthening span of life has meant the submission to operation of more old people than ever before and in them the outcome may well be governed not by the main disease or by factors within the surgeon's control but by such considerations as the cardiovascular status or the ability of the kidney the liver or the adrenal glands to accept the added strain of any surgical procedure Our relatively crude methods of pre operative survey are not yet sensitive enough to permit accurate assessment of such extraneous risks

Classification of Post Operative Deaths—In the privacy of our own councils and for our own profit we sought to separate our post operative fatalities into unavoidable and avoidable deaths

Unavoidable Deaths—These deaths were due to the advanced state or the inevitable progress of the disease to the presence of lethal coexisting disease or to the development of an unpredictable—and uncontrollable—lesion such as coronary thrombosis or cerebral hæmorrhage

If these criteria are acceptable then 116 of the deaths after operation (Table II) were frankly unavoidable and need no more than a passing glance

It will be noted that advanced malignant disease accounted for nearly two thirds (72 deaths or 62 per cent of the total) and the chief offenders were cancer of the colon and rectum (28 cases) of the stomach (10 cases) and of the gallbladder and bile ducts (10 cases)

Most of the colon and rectal cancers in this category were admitted in subacute or acute obstruction and in the majority some palliative type of operation was possible On review it is my impression that delay in diagnosis and in treatment was more often due to the patient than to the medical attendant Early changes in bowel habit abdominal uneasiness the appearance of a little blood in the lavatory pan after defæcation were all too frequently neglected until more imperative symptoms appeared Carcinoma of the cæcum was an exception however for here the insidious loss of health or the sense of intolerable fatigue had sometimes driven the patient to the practitioner early and a casual diagnosis of bloodlessness and the exhibition of iron had satisfied both until a tumour mass was palpably obvious and the disease incurable If this large group of advanced and hopeless colon tumours is taken into account the results of the treatment of cancer of the large bowel are most disappointing—all the more so because the development of safer methods of pre operative bowel preparation and of anastomosis have gone far to eliminate the operative hazards of a former day

Five of the group of advanced malignancies were cancers of the gallbladder and as usual the tumour was associated with gallstones which had produced only trifling inconvenience Thus in one patient an attack of acute cholecystitis some twelve years before had passed off with no pronounced after effects and though investigation after the

acute attack had demonstrated a completely non functioning gall bladder, the patient was advised to leave well alone It was on the eve of her retirement from a busy teaching post that she was stricken with malignant jaundice, and was found at operation to be beyond surgical aid

TABLE II

Unavoidable Deaths—116

Advanced Malignant Disease—72	
Colon and rectum	28
Stomach	10
Gallbladder and bile ducts	10
Pancreas	7
Breast	5
Œsophagus	2
Buccal cavity	1
Bladder and prostate	2
Skin	1
Liver	1
Sarcomas	5
Cardiovascular Diseases—16	
Peripheral gangrene	10
Coronorary thrombosis	4
Mesenteric thrombosis	2
Trauma—7	
Fractures	4
Multiple injuries	3
Acute Infections—12	
Gallbladder	2
Liver	3
Peritonitis (including tuberculosis)	3
Phagœdenic ulcer of thigh	1
Senile ulcerative proctitis	1
Subcutaneous infection with severe diabetes	2
Miscellaneous—9	
Cirrhosis of liver	2
Malignant hypertension	2
Uræmia	4
Thrombocytopænic purpura	1

The regular association between gallstones and carcinoma of the gallbladder must inevitably direct our attention to the problem of the 'silent biliary calculus for gallstones are not infrequently discovered in routine radiographic examination of the chest or of the spine in patients without sharply etched biliary symptoms Close questioning will often reveal that in fact these stones are less innocuous than they seem and the late Dr W J Mayo is credited with the observation that there was no such thing as a completely silent gallstone

The relative frequency of gallstones and the comparative rarity of carcinoma of the gallbladder hardly justify the argument of potential

malignancy in advising operation in mild or symptomless cholelithiasis but biliary calculi have other dangerous sequelæ—obstructive cholecystitis intestino biliary fistula gallstone ileus and obstructive jaundice In our most recent patient with gallstone ileus the calculus had been observed in the course of a radiological examination of the lumbar spine some fifteen years before and although there was a distinct possibility that the back pain was of biliary origin he was strongly advised to keep out of the clutches of the surgeons When finally, after three days of acute small bowel obstruction he had equally strongly to be urged in the reverse direction his fate was sealed for the ileus—as is so often the case with gallstone obstruction—proved lethal

It is unfortunately true that the complications of gallstones occur most frequently in the elderly when the result of operation may be jeopardised by other factors It is worth emphasis therefore that apart from age the hazard of operation on the biliary tract is that imposed by these very complications—by obstructive jaundice and the consequent need to drain the common bile duct by the disablement which a combination of obstruction and sepsis can inflict on the liver parenchyma and by malignant disease with its early spread to the liver and the porta hepatis On the other hand the risks of cholecystectomy in uncomplicated biliary disease are negligible and the case for earlier surgery seems to be unanswerable

Avoidable Deaths —In those that we styled the avoidable post operative deaths the selection the nature the extent or the duration of the operation the choice or execution of the anæsthetic or the management or circumstances of the post operative state contributed in some way to the fatal outcome They were therefore avoidable though not in the narrow sense that the surgical management was incorrect inadequate or unwise in every instance Some certainly were due at least in part to errors of judgment or of technique but in many the fatal issue was determined solely by mechanisms that are still relatively obscure and that though patently initiated by operation are strictly speaking unavoidable in the present state of our knowledge

It is this last group that provides one of the principal challenges of modern surgery and if at the moment such disasters as pulmonary embolism and hepatic failure are largely beyond our understanding and our control there is at least some prospect that they will ultimately be mastered and become in fact preventable

In this series the deaths directly related to the surgical treatment amounted to 95 or 1 4 per cent of the total operations and they could be arranged in a number of well defined groups (Table III) Certain of them need no more than a brief notice

Anæsthetic Deaths —In four patients death was the direct result of anæsthesia In two fatal asphyxia resulted from the aspiration of intestinal contents in the induction phase in another death occurred suddenly during an injection of sodium pentothal in an elderly subject

in whom the drug is certainly dangerous and in the last a case of nodular goitre which had recurred after two previous operations there was sudden and massive pulmonary collapse a few hours after operation as a result of obstruction of the respiratory passages by a large quantity of sticky mucus

The direct anæsthetic hazard was therefore insignificant, and in this series it might have been reduced even further Thus, the necessity for gastric lavage and intestinal intubation before an emergency abdominal operation was well appreciated, but in one patient, the *precaution was frankly omitted, and in the other*, a tube introduced in the ward was inadvertently withdrawn, and a hurried attempt at reinsertion was unsuccessful

TABLE III

Avoidable Deaths—95	
Surgical errors	29
Pulmonary embolism	19
Peripheral circulatory failure	[illegible]
Liver failure	12
Anæsthetic deaths	4
Post operative pulmonary complications	4
Effects of transfusion	3
Cardiovascular complications	2

In addition to the deaths directly due to it the anæsthetic was possibly a factor in certain of the other fatal cases Thus in the group of respiratory complications were two patients who underwent gas*trectomy on the same winter morning and who by the following day* had each developed an obvious and overwhelming pulmonary infection which had almost certainly originated in post operative atelectasis In neither case had post operative bronchoscopic aspiration been carried out but since this experience the manœuvre has been a routine practice before the patient leaves the theatre after major upper abdominal operations It cannot be claimed that it has abolished respiratory complications but since its introduction there has been only one death from an acute pulmonary condition and that in an elderly frail and very ill woman whose gallbladder had perforce to be drained on account of acute gangrenous cholecystitis

The two *cardiovascular deaths* each a proven example of post operative coronary thrombosis were included in the avoidable series because the operation was possibly contributory In the first the thrombosis developed immediately after splanchnicectomy for hypertension under high spinal anæsthesia and in the other it followed a somewhat protracted and difficult gastrectomy for bleeding stomal ulcer The patient had undergone operation for perforation of a duodenal ulcer and later had had a gastro enterestomy established Following gastric resection she appeared to be making a good recovery until her sudden and fatal collapse but autopsy showed advanced chronic myocardial disease as well as acute coronary occlusion The

operation was long tedious and difficult and it could not be completely exonerated

The occurrence of three *transfusion deaths* is a reminder that though the contribution of blood and plasma infusion to the scope and the safety of modern surgery is beyond question as well as beyond praise the procedure itself is not yet entirely free from risk The plasma death was particularly unfortunate for the patient had undergone a resection of the lower end of the œsophagus for carcinoma and in order to gain proper access for the abdominal part of the operation it was necessary to remove a massively enlarged uterus studded with giant fibroids The administration of plasma on the following day was prompted not by any specifically declared need but by a desire to supply a source of protein from the beginning of convalescence The reaction to the first bottle of reconstituted dried plasma was severe and fatal within a few hours the clinical picture suggested a sudden catastrophe such as a suprarenal apoplexy or a coronary infarction but autopsy failed to demonstrate a recognisable cause of death Fatalities following the use of dried plasma and closely resembling this were encountered from time to time during the war especially in the tropics and since this added civil experience the infusion of reconstituted plasma has been avoided in the unit

The other transfusion deaths followed the administration of whole blood In one the cause of the reaction was not discovered but in the other the blood was subsequently found to be infected The rarity of such an event is a tribute to those who conduct this vital and important service so admirably

The remaining groups of the so called avoidable deaths were each of considerable interest and importance and deserve a closer scrutiny

The Surgical Errors —The first series were attributed after reflection to errors on the part of the surgeon an opinion which in some instances was unquestionably harsh but possessed the virtue of defining the possible contribution of the operator himself to a further reduction in surgical mortality

There were 29 patients (0 56 per cent of the total operations) in whom in the light of eventual experience either too much or too little was attempted in whom treatment was delayed beyond the optimum time or in whom a frank post operative complication such as infection or obstruction developed (Table IV)

Inadequate or Excessive Surgery —In this group the adequacy of the surgical management was in question Thus in two fatal cases of regional enteritis the disease was discovered in the course of an emergency operation and the lesions were left well alone The consensus of surgical opinion still favours this policy but in the first of our patients a regional jejunitis subsequently progressed to gangrene and in the second an ileocæcal lesion eventuated in peritonitis and death It is just possible that a bolder approach in the shape of

immediate resection, might have had a happier outcome, and for this reason we felt obliged to regard these deaths as due to inadequate surgery

TABLE IV

Surgical Errors—29

Inadequate or Excessive Surgery—6	
Acute regional enteritis	2
Diverticulitis	1
Volvulus of the pelvic colon	1
Liver abscess	1
Acute cholecystitis	1
Delayed Surgery—4	
Ulcerative colitis	3
Peptic stricture of the œsophagus	1
Technical Complications—19	
Intraperitoneal Leaks (12)	
Following—	
Total gastrectomy	2
Partial gastrectomy	6
Gastroscopy	1
Restorative resection of rectum	2
Closure of colostomy	1
Post Operative Infections (4)	
Pancreatitis following gastrectomy	1
Pancreatitis following choledochostomy	1
Retroperitoneal cellulitis following choledochostomy	1
Burst abdomen	1
Post Operative Obstruction (2)	
Following—	
Gastrectomy	1
Cholecystenterostomy	1
Post Operative Infarction of the Gut (1)	
Following Reduction of volvulus of midgut	1

In the other deaths in this class there was again no certainty that a fatal issue could have been avoided but again, the treatment adopted was open to criticism The errors comprised —

1 Failure to establish a colostomy at laparotomy in a patient with acute diverticulitis of the pelvic colon The subsequent perforation and fatal peritonitis might thus have been prevented
2 Failure to recognise the precarious state of the constriction rings after reduction of a volvulus of the pelvic colon
3 Failure to discover a secondarily infected amœbic liver abscess
4 The submission of a woman up in years to cholecystectomy *rather than to simple drainage for acute suppurative cholecystitis*

Delayed Surgery—In a number of patients delay in resorting to surgery may well have prejudiced the issue

In one case death resulted from repeated massive hæmorrhages from an unsuspected gastric ulcer while the man was under treatment

for dilatation of a peptic stricture of the œsophagus and earlier gastrectomy might have prevented this and also improved both the œsophagitis and the stenosis

The other patients were victims of ulcerative colitis and it may have been unduly self critical to attribute their deaths to delayed surgery For this formidable and tragic disease raises problems of the greatest complexity and anxiety Earlier reference was made to two patients who died from the progress of the disease without operation and a survey of these five cases serves to define the major problems confronting the surgeon charged with the management of ulcerative colitis

Ulcerative Colitis and its Management—In all five instances the patients suffered from the acute fulminating type of the disease and there is general agreement that in this group it is particularly difficult to determine the exact timing and the exact scope and nature of operative intervention In the subacute and chronic types the position is otherwise for few would challenge the propriety of operation when repeated relapses threaten a life of chronic invalidism or when life is jeopardised by such complications as extensive bowel hæmorrhage or by stricture of the colon and rectum

In acute progressive ulcerative colitis however the patient steadily loses ground, and there are profound nutritional electrolyte and vitamin disturbances from malabsorption and from the profuse purulent diarrhœa The crux of the problem is whether this continuous deterioration can be arrested by surgery—and up to the present surgery has meant the establishment of an ileostomy This was attempted in two instances in each the colon had perforated in several places and in one the ulcerative process had involved not only the colon but practically the entire small intestine In the two patients who died without operation there were again multiple perforations In all four an attempt had been made to improve the general state as a prelude to operation and it was this period of delay which was open to criticism

In the last case operation was undertaken promptly The patient a nursing sister was seriously ill when the ileostomy was made and there was a short lived phase of improvement following it Perhaps wrongly resection of the colon was postponed in an effort to restore her general condition When this failed and the situation was nearly desperate the right half of the colon was removed but following the ileostomy the bowel had perforated in several places, and there was well marked peritonitis

This experience suggested that in fact ileostomy was by no means certain either to stay the progress of the disease or to prevent perfora tion a view that found some support in the behaviour of another patient now well following staged excisions of the entire colon and rectum In this young woman there was a sudden and serious exten sion of the disease to the previously uninvolved cæcum and ascending

colon many months after ileostomy had been performed as the first step in surgical treatment

It is difficult to avoid the conclusion that some reorientation of our attitude to ileostomy is needed If the operation is not life saving it would be justifiable to supplement it by simultaneous partial resection of the colon which would carry only a negligible if any additional operative risk The arguments against such a policy that ileostomy alone is sometimes curative, or that after a time it might be possible to restore the continuity of the bowel need not be seriously entertained The grossly ulcerated colon of unrelenting ulcerative colitis can never recover sufficiently to become a safe or a useful companion at best healing leaves a rigid, inert pipe stem colon which is merely a conduit and not a reservoir while at worst the mucosal regeneration may assume the form of polypoidal excresences—pseudo polyposis—which have a definite association with malignant degeneration

The case for early and radical surgery in severe ulcerative colitis appears to be a valid one therefore and because it is so our fatal cases in this series were classified as deaths which might possibly have been avoided *In the event our strategy failed to influence the course of the disease*

Technical Complications —The fatal technical complications comprised a number of intraperitoneal infections and post operative mechanical obstructions (Table IV) Not all of them were necessarily the result of errors either of commission or omission and some were unexpected inexplicable and unpreventable It is unfortunately true that on occasion even the most careful of surgeons is not immune to misfortune or disaster His medium is living tissue subject to numberless and complicated biological influences about which we are still imperfectly informed In other crafts—of wood and clay of metal and stone—a given series of manœuvres may be expected to yield a predictable result varying only with the skill of the craftsman A surgical operation on the other hand initiates a group of complex and dynamic phenomena and the response is sometimes variable and occasionally perverted and unexpected Thus dehiscence of laparotomy wounds the development of obstruction from widespread peritoneal adhesions and some types of intraperitoneal infection are frequently outwith the operator s control

The catalogue (Table IV) is sufficiently explanatory to make detailed comment unnecessary in the majority of cases but some merit brief notice

The lethal infarction of the gut followed the reduction of a chronic volvolus of the midgut in a girl of 17 years who was grossly undersized and undernourished as a result of a secondary malabsorption syndrome There had been countless attacks of acute obstruction and at operation a number of completely fibrosed vessels were observed in the thickened mesentery The intestine was certainly viable when the abdominal wound was repaired but infarction of the small gut in the

whole territory of the superior mesenteric artery supervened rapidly It is just possible that the disaster might have been avoided by prophylactic anticoagulant therapy

The two fatal post-operative obstructions were due to operative faults In the first the occlusion resulted from the kinking of the efferent loop of a cholecyst jejunostomy and could have been prevented by supplementary entero-anastomosis in the other torsion had also occurred at the site of an œsophago jejunal anastomosis following total gastrectomy

No fewer than seven of the remaining deaths followed the operation of partial resection of the stomach and since this operation contributed five additional deaths it must be submitted to closer scrutiny

The Hazards of Partial Gastrectomy —During the quinquennium partial gastrectomy was undertaken for simple ulcer in 250 patients of whom 10 died At first sight the overall mortality appears unduly high but there were a number of unusual and unexpected complications (Table V) and it would not be proper to condemn the operation

TABLE V

Fatal Complications of Partial Gastrectomy

Intraperitoneal leaks	4
Shock	1
Acute pancreatiti	1
Pulmonary complications	2
Pseudomembranous enteritis	1
Adrenal tuberculosis	1

on account of the mortality in this small series Thus pulmonary complications of such overwhelming virulence are exceedingly rare in these times and the deaths due to acute adrenal failure from unsuspected tuberculous destruction of the gland and from pseudo membranous enteritis are almost unique The death from shock was frankly so classified for lack of a more adequate explanation for death was preceded by a series of transient but severe episodes of collapse before the final circulatory failure and no abnormality other than coronary degeneration was identified at autopsy

The fact remains that in this unit a disconcerting number of deaths (2 per cent) were directly due to technical complications In two of them leakage occurred from the duodenal stump in one instance the end of the duodenum was found at autopsy to be completely open suggesting a blow out secondary to some mechanical difficulty at the gastric stoma In the other the duodenal closure was sound but leakage had occurred from the anterior duodenal wall where an area of necrosis had developed At this time removal of the duodenal ulcer was practised as a routine no matter how difficult the dissection or how extensive the amount of mobilisation demanded Such a practice may well jeopardise the blood supply of the duodenal wall

and latterly the ulcer has been left behind when the local conditions have been particularly unfavourable

The other leaks were from the neighbourhood of the gastro jejunal anastomosis in one instance and from the antral remnant after Bancroft's operation, an experience which others who have used this method have shared

The balance sheet of gastrectomy is not balanced simply by disclosing its overall mortality however There is growing uneasiness about its late effects also for the functional result leaves something to be desired in a disturbing number of patients Few would dispute its virtues in the management of peptic ulcer of the stomach and most claim that at the moment, and with all its faults, it is the best answer to the problem of the duodenal ulcer The truth of this assertion must be determined by each surgeon for himself however and it is proper to remind ourselves that the much abused gastroenterostomy was not abandoned because it failed to cure duodenal ulcer It did so permanently in the large majority of patients and it fell into disrepute, not so much because of the high incidence of subsequent stomal ulcer but because of the high mortality attending the secondary operations The position is different to day for the death rate following operation for stomal ulcer is not appreciably greater than that for primary gastrectomy Most stomal ulcers develop in the first three or four years after gastroenterostomy, so that if the addition of vagotomy can effect a substantial reduction of acidity only during this danger period, the incidence of gastro jejunal ulceration might well be reduced to insignificant proportions Even if a number have to be submitted to gastrectomy later, the final balance might well be loaded in favour of the simpler and safer procedure if regard is paid to the mortality of gastrectomy to its small but definite recurrence rate, to its post operative discomforts its dumpings its bilious vomitings and to its occasional intractable anæmias

This is no doubt unfashionable heresy but I believe that the thoughtful surgeon should constantly re examine his attitude to gastrectomy and in the light of his own results both fatal and functional rather than those of some persuasive technical genius who if statistics are credible is immune to even the most fortuitous accidents that befall his humbler fellow craftsmen At the moment, there is cause neither for satisfaction nor complacency and certainly not for continued unthinking advocacy of gastrectomy for any and every duodenal ulcer

Pulmonary Embolism —The fact is tragic but incontestable that increasing clinical vigilance for the evidences of peripheral venous thrombosis the introduction of the anticoagulant drugs and the cult of early rising after operation have alike failed to eliminate pulmonary embolism as a serious operative hazard A few years ago in the first flush of enthusiasm over heparin the occurrence of a fatal embolus was to some a matter of reproach—an evidence either of carelessness ignorance or lack of clinical acumen Subsequent investigations have

prompted a less emphatic approach and of late years, no surgical danger has so much engaged the attention of clinical research workers as the thrombo embolic phenomena

In this series, fatal pulmonary embolism occurred on 19 occasions and was the sole cause of death in another instance an embolus was partly responsible, but the actual cause of death was coronary thrombosis This single complication therefore, contributed a little over 20 per cent of the potentially avoidable deaths and its incidence in the whole group of operations was 3 8 per thousand

The relation of fatal to non fatal pulmonary infarction was not worked out for the whole series, but my colleague Mr Gordon McNaught made a special study of 1004 consecutive cases over an eleven month period and in this small group lung embolism occurred on 20 occasions 6 of which were fatal Three of the patients had not been submitted to operation a reminder that the problem is not a surgical one alone but inseparable from any illness—or trauma—demanding rest in bed The wards in which these patients were treated were as thrombosis minded ' as most in so far as routine post operative examination of the calves for tenderness and of the ankles for œdema was the rule, there was a comprehensive programme of early post operative activity and the slightest suspicion of phlebo thrombosis was met by the immediate exhibition of anticoagulant drugs

That this obviously was not enough was evidenced by the fact that in one third of the fatal cases and in a like proportion of non fatal cases, the lung embolism was the earliest clinical indication of thrombosis The existence of a group of clinically silent thromboses was supported by the site incidence of the initial clotting as determined at autopsy for while the femoral tibial and calf veins were the most common source no fewer than a quarter originated in the pelvic veins or in the inferior vena cava

On the other hand we have been misled by the presence of calf tenderness into the unnecessary administration of anticoagulants though fortunately with severe consequences on one occasion only This patient was convalescing from splanchnicectomy for hypertension when an incident of dyspnœa occurring she was discovered to have tender calves, and pain on dorsiflexion of the ankles Heparin administration was immediately begun but after forty eight hours she collapsed with all the evidences of peripheral circulatory failure and died in a few hours Autopsy failed to demonstrate either a pulmonary embolus or any peripheral phlebothrombosis but there was a large intra thoracic hæmorrhage

There are many facets of this interesting and important problem that I am not competent to discuss but since this is in the main a factual report it may be appropriate briefly to record certain experiences which gave us some food for thought

The several benefits of the modern post operative regime of early movement in bed regular breathing exercises avoidance of the Fowler

and similar positions and insistence on early rising are not to be disputed that such measures have specifically diminished the liability to thrombosis or reduced the incidence of pulmonary emboli is open to serious question however Thus an elderly woman, an out patient reported with a subacute breast abscess which was incised under pentothal anæsthesia in the early afternoon She spent the remainder of that day in bed, but was up on the following day On the eighth day, a small pulmonary embolus developed and on the eleventh day, despite heparinisation a larger embolus occurred, from which fortunately, she made a good recovery Again, a middle aged woman was submitted to cholecystectomy for flatulent dyspepsia and a poorly functioning gallbladder which was found at operation to be normal She was small stout and lethargic and as she was thought though without valid reason to be a likely candidate for phlebothrombosis her post operative management was particularly vigorous Her convalescence was uneventful however and she was discharged in the usual time Some six weeks after her return home while cleaning her fireplace she was stricken with a massive pulmonary infarct which was all but fatal

Such episodes—and others like them—have convinced us that though there may be sound enough reasons for a post operative programme of forced activity it does not inhibit thrombosis or prevent embolism

Soon after the introduction of heparin there was a pious hope—and sometimes an arrogant assertion—that there would be no excuse for fatal pulmonary embolism for early diagnosis and energetic treatment were bound to be successful The passage of time has confirmed the efficacy and the value of the anti coagulant drugs but it is now obvious that unless they are exhibited in the first few hours they are by no means protective against later pulmonary embolus Thus a man aged 65 was admitted with a gluteal abscess which was drained by incision and improved rapidly He was up and about in the ward by the seventh day when he complained of breathlessness There was no clinical evidence of thrombosis but on the following day he complained of pain in the right calf Anticoagulant therapy was then begun under strict laboratory control but two days later and only half an hour after an injection of heparin he complained of pain in the right thigh Four days later there was evident thrombosis in the left femoral vein and there were frequent attacks of cyanosis and breathlessness His condition continued to be poor and twelve days after the original attack of dyspnœa he succumbed to a massive embolus The autopsy revealed clots in both femoral veins and in addition to a recent thrombus which straddled the bifurcation of the pulmonary artery there were numerous small infarcts in both lungs

This too was not an isolated experience and it would appear that even when a diagnosis of thrombosis has been made and therapy begun the prognosis should be on the most guarded lines

In this series, the premature withdrawal of the anticoagulants was responsible for another tragedy A cup arthroplasty of the hip had been carried out for intrapelvic protrusion of the acetabulum in a woman 35 years of age The possible significance of a short period of persistently raised pulse rate as an indication of potential thrombosis was not appreciated perhaps because there was a slight and superficial wound infection It was possible to begin intensive physio therapy on the fourteenth day however and progress was steady until the twenty-eighth day when there was a sudden pulmonary embolus Anticoagulant therapy was immediately begun and she made such a good recovery that the anticoagulants were discontinued after eight days Her conditions gave no further cause for anxiety until the fortieth day, when without warning there was another sudden and rapidly fatal episode It is probable that death could have been averted by prolonging the administration of anticoagulants until the patient was again ambulant

There is a prevalent clinical impression that thrombosis and embolism are on the increase However debatable this may be I believe that careful clinical observations leave no doubt that small lung emboli are even more common than we imagine now and that some at least of the more obscure post operative pulmonary compli cations are almost certainly embolic

It is difficult to estimate its relative frequency from decade to decade McNaught investigated the incidence of pulmonary embolism at autopsy in the pathological service of the Royal Infirmary of Edin burgh over a twenty one year period and found a mean annual incidence of 1 6 per cent with a standard deviation of ±0 64 per cent The present group—20 out of a total of 95 post operative deaths is admittedly incomparable but if it be assumed that none of the other deaths operative or non operative was due to pulmonary embolism the incidence is slightly over 7 per cent This appears to support the common clinical impression but impressions are notoriously dangerous and regard must certainly be paid to the extent and severity of present day operations to the fact that the average hospital ward population is considerably older and to the greater frequency with which autopsy examination is sought Nevertheless the view that there is a real increase is supported by the comprehensive survey of thrombo embolism in the hospitals of New Orleans by Ochsner and De Bakey

At the moment our urgent need is for a policy which will reduce the morbidity and the mortality of this disaster The evolution of a laboratory test which would enable the likely thrombotics to be identified and energetically treated with anticoagulants from the start would be a notable advance but several such tests have been tried out in the past few years without success

The alternative—the routine prophylactic administration of the anticoagulants—is both costly and time consuming in view of the need

for accurate laboratory control In the meantime we have no option but to rely on clinical vigilance with prophylactic treatment reserved for patients who give a history of previous thrombotic disease such as "white leg," and energetic therapy at the least suspicion of trouble—a spike of unexplained fever on the fourth or fifth day a puzzling rise in pulse rate an attack of painful breathlessness or the discovery of pain and tenderness in the calves The position is far from reassuring however, and a fresh approach is needed to this difficult and dangerous problem

Liver Deaths—It is common experience that, after operations on the gallbladder the pancreas, and their ducts a number of patients die from hepatic failure In this series there were 12 such deaths and the diseases demanding operation were carcinoma of the pancreas and ampulla (4 cases) chronic pancreatitis suspected to be tumour (2 cases) and stone in the common bile duct (6 cases) In each of these patients no other lethal complication was identified at autopsy

The clinical picture was far from uniform but it was possible to recognise three distinct groups In the first, death occurred promptly after operation Post operative consciousness was short or not regained and hyper pyrexia peripheral circulatory failure and coma accompanied by an assortment of neurological signs, and by a characteristic odour in the breath—the fœtor hepaticus —were the outstanding clinical evidences Liver necrosis was the only notable autopsy finding

Four deaths were of this type and a typical case was that of a male patient aged 70 in whom stones had been removed from the common bile duct He was returned to the ward in excellent condition after a relatively easy operation but in eight hours there was a marked rise in temperature and pulse and by the twelfth hour there was obvious failure of the peripheral circulation The temperature was then 107° F and the blood pressure 60/50 Death in coma took place some twenty hours after operation At autopsy the liver looked remarkably normal to the naked eye but on histological examination the hepatic cells were granular and so swollen that the sinusoids were compressed there was also a diffuse fatty change practically every cell examined containing at least one fat vacuole and the portal tracts were infiltrated by lymphocytes There was no evidence of acute cholangitis

In the second type of liver failure the patient apparently makes a satisfactory initial recovery but the urinary output is low from the start and finally there may be complete anuria Degenerative changes may be present in the renal tubules in addition to the liver necrosis Four of the deaths belonged to this group sometimes styled the hepato renal syndrome only two of them developed renal failure however so that presumably the renal phase is neither an essential nor the lethal part of the syndrome

The typical sequence of events is well illustrated by the case of a male patient, aged 65 who after an obstructive jaundice which had lasted three weeks underwent a duodeno pancreatectomy for carcinoma

of the head of the pancreas The operation was not particularly difficult and the only incident of note was a period of about an hour and a quarter when the blood pressure fell from its general level of 140/80 to 80/60 On his return to the ward the pressure had resumed its pre operative level and for the first forty eight hours his condition was satisfactory Only 30 ml and 6 5 ml of urine were collected on the first and second days respectively, however, and there was a steady rise in the blood urea nitrogen which reached a level of 117 mgm per cent by the third day Thereafter there was no further secretion of urine and he gradually deteriorated to die in coma at the end of seventy two hours

Examination of the liver showed commencing disruption of the lobular architecture lymphocytic infiltration of the portal tracts and a widespread fatty change in the cells of the centri lobular region The pathological diagnosis was early biliary cirrhosis The renal pathology was not typical of the distal tubular degenerations encountered in the various states of shock, but the tubules contained an amorphous acidophilic precipitate and the pathologist s diagnosis was cholemic nephrosis

The third type of liver death which was encountered in this series ran a more protracted course with gradual decline in health, with increasing weakness deepening jaundice hæmorrhages purpuric skin eruptions apathy and generalised œdema The terminal phase was heralded by increasing drowsiness and ultimately coma and death supervened

The factor common to all these patients was jaundice but this was so variable both in duration and in degree that neither seemed to bear any definite relationship to the development of the syndrome or to the clinical form it assumed Furthermore patients with jaundice as severe or even deeper and of as long or even longer standing were successfully submitted to operation without so much as a threat of liver failure This suggests that the liver failure is dictated not so much by the new circumstances—of biliary obstruction for example—as by the presence of pre existing and undetected liver damage which leaves the parenchyma incompetent to resist the further insult of operation Heyd who originally described the syndrome of the liver death believed that the partially damaged liver produced a lethal toxin others have suggested that the debased parenchyma is unable to detoxicate a metabolic poison produced in the splanchnic area under the impress of trauma anæsthesia shock infection or hæmorrhage It may well prove hardly necessary to postulate either an exogenous or endogenous toxin to explain the liver death however The hepatic parenchyma has wide and protean functions and on its health and capacity depend many of the vital processes of nutrition and the complicated mechanisms of intracellular metabolism and the impact of the further insult of operation in the liver weakling may well give rise to a death which is metabolic rather than toxic That the

ætiological factor is not in every case unrelenting and indeed not particularly complex is evidenced by the occasional rapid and spontaneous return of consciousness and that speedy disappearance of the neurological signs which is amongst the most startling of clinical phenomena

The elucidation of the liver death and of hepatic coma may well be matters for the biochemist to the surgeon, faced with the necessity for operation, it is of the greatest moment that out of the present researches there should emerge a reliable test of liver function that means should be devised to counter the harmful effects of operative trauma and that from the mass of metabolic studies a rational therapeutic management should be evolved

Some part of the way towards this goal may even now have been travelled Thus we appreciate the danger to the liver parenchyma of anoxia whether due to shock to anæsthesia to operation or to hæmorrhage and if it cannot always be avoided—as in the protracted manipulations of a radical pancreatectomy—it can be kept to a minimum both of degree and of time

Until recently the onset of liver failure was almost invariably the herald of impending death This gloomy picture has been lightened a little bv the researches of Latner in Newcastle He has proposed and elaborated a regime designed to supply by intravenous infusion a comprehensive range of the essential vitamins with amino acid and with fluid and electrolytes during the period of hepatic coma Conceived as a kind of replacement or substitution therapy it is intended to maintain the metabolic processes of the body during the time when the liver with its rapid power of recovery is trying to effect its own repair

The apparent efficacy of Latner s treatment was demonstrated by the case of a female aged 49 who was admitted to the medical division with obstructive jaundice Her condition rapidly deteriorated and she became drowsy and difficult to rouse muscular twitchings were prominent and the fœtor hepaticus all pervading In the considered opinion of both medical and surgical observers the outlook was hopeless Nevertheless operation was advised because a mass in the upper right quadrant of the abdomen was thought to be an abscess or a large empyema of the gallbladder It was in fact an abscess there was not a stone in the common duct but the duct and the upper border of the duodenum formed part of the abscess wall Cholecystectomy was completed and the bile duct drained The patient did not recover complete consciousness after operation instead she passed into coma and the Latner regime was resorted to but without much confidence For two days her condition remained unchanged but abruptly thereafter there was a decided and rapid improvement and it was possible to discontinue the intravenous infusion after five days The subsequent convalescence was not without incident but her eventual recovery was satisfactory Since spontaneous and dramatic recovery from hepatic

coma with complete and almost instantaneous reversal of the neurological signs is a rare but possible event it would be unwise to claim too much for Latner s infusion on the strength of a single case but my own experience and that of other observers did not include an example of recovery from so desperate an illness On several occasions since then there have been encouraging experiences with the method and it may be that in the future the liver deaths will feature less prominently amongst the fatal complications of gallbladder surgery

TABLE VI

Causes of Fatal Peripheral Circulatory Failure

Hæmorrhage	5 cases
Following—	
1 Pancreatoduodenectomy for carcinoma of pancreas	
2 Splanchnicectomy for hypertension	
3 Choledochostomy (from unsuspected duodenal ulcer)	
4 Gastrectomy for massive bleeding from gastric ulcer	
5 Gastrectomy for massive bleeding from gastric ulcer	
Toxic and Infective Shock	cases
From—	
1 Peritonitis	
2 Late perforated duodenal ulcer	
Late Mechanical Intestinal Obstruction	cases
1 Strangulated femoral hernia	
Gallstone ileus	
Paralytic Ileus	5 cases
Following—	
1, 2 } Volvulus of pelvic colon	
3 Band obstruction of small intestine	
4 Strangulated femoral hernia	
5 Acute appendicitis	
Unexplained Circulatory Failure	1 case
Following Gastrectomy	
Hyperthermia	1 case
Overheating following arthrodesis of the knee	
Acute Adrenal Failure	4 cases
1 Massive adrenal hæmorrhage following transfusion	
Massive adrenal hæmorrhage following gastrectomy for stomal ulcer	
3 Depletion of cortical lipoid following appendicectomy for acute appendicitis	
4 Adrenal tuberculosis complicating gastrectomy for gastric ulcer	
Post Operative Necrosis of the Intestinal Mucosa	2 cases
Following—	
1 Gastrectomy for duodenal ulcer	
2 Gastrectomy for stomal ulcer	

Peripheral Circulatory Failure—In 22 patients death was due to failure of the peripheral circulation from miscellaneous causes (Table VI) Thus hæmorrhage was the mechanism in 5 instances advanced peritoneal infection in 2 and late mechanical obstruction of the intestine in a further 2 patients they need no further discussion

Paralytic ileus was fatal in 5 patients despite energetic efforts to

overcome it In each case autopsy confirmed the absence of peritonitis or of a mechanical obstruction each was vigorously treated by gastric suction and by fluid and salt replacement, but with no attempt to cater for special electrolyte requirements In retrospect it seems more than likely that the lethal factor was an uncorrected high grade potassium deficiency, and, in extenuation it is only fair to recall that our apprecia tion of the importance of potassium is of comparatively recent origin

The circulatory collapse following gastrectomy belonged to that mysterious category of post operative deaths in which autopsy fails to establish a satisfactory explanation, it was referred to earlier in this report

The dangers of too enthusiastic resuscitation were all too evident in the patient who died following arthrodesis of the knee joint for tuberculosis Radiological confirmation of the satisfactory position of the bones was sought before the patient was returned to the ward from the theatre There was some delay in the Radiological Depart ment, and when she was eventually put to bed, she was cold and clammy This was the signal for exposure to the radiant heat of a cage equipped with a formidable battery of high powered bulbs In this inferno she lay for some hours death occurred in hyperpyrexia on the same evening

Acute Adrenal Failure—On four occasions sudden and rapidly fatal circulatory collapse was due to acute adrenal failure Our first experience of this was in a female civil servant, aged 27 years who was transferred from the medical division for operation for ulcerative colitis The post operative recovery was satisfactory and the patient had so far improved that she was allowed up on the twelfth day On the twentieth day there was a mild attack of enteritis and although her general condition was not giving rise to anxiety a transfusion was decided upon largely as a prophylactic A slow blood drip was begun at 11 45 a m and at approximately 1 15 p m when the transfusion was almost completed she complained of severe pain in the back The infusion was immediately stopped but the pain became progressively more severe and at 2 o'clock she suddenly lapsed into unconsciousness Respirations were laboured and there was facial cyanosis the temperature was 100 the pulse rate 130 per minute and the blood pressure 60/40 Every available stimulant was employed in an attempt at resuscitation but by 2 30 p m the peripheral pulses had disappeared and the blood pressure was unrecordable Death took place in coma at 2 a m the following morning

At autopsy there was extensive hæmorrhagic destruction of the medulla, and to a lesser and patchy extent of the cortex of both adrenal glands Death was therefore due to circulatory collapse from acute adrenal failure but the explanation of the massive adrenal hæmor rhages was not obvious A precisely similar syndrome with hæmorrhagic destruction of the adrenals is sometimes encountered in meningococcal septicæmia (the Freiderich Waterhouse syndrome)

and in pregnancy In this instance the Transfusion Service was able to exclude infection and all agglutination tests were negative Never theless the accident must be regarded as an unusual and fortunately a rare complication of the transfusion

The other examples of acute adrenal failure were more directly related to operation and though the pathological changes in the adrenal gland varied there was the same dramatic and irreversible circulatory collapse

These complications have perhaps a particular interest and a particular significance at the moment It has been suggested that in response to injury—in its broadest sense—there is a specific body reaction which is mediated by the pituitary and the adrenal glands and which culminates in an increased production of adrenal cortical hormones Inability to respond normally may be the result of pre existing disease and in one of our own patients in whom the classical circulatory failure developed some days after gastrectomy the adrenal glands were the site of extensive tuberculous infection

On the other hand failure to respond may be due to the severity or the duration of the stimulus or to an individual adrenal incompetence It has been shown experimentally that under circumstances of profound shock a variety of changes occur in the adrenal glands including disappearance of lipoid from the cortex necrosis and hæmorrhage Examples of several of these changes have been encountered in other of the present series of deaths but in those we have called the adrenal deaths the adrenal pathology was the most prominent autopsy finding

The recent demonstration that adrenaline by way of pituitary and hypothalmic stimulation normally induces an increased production of the cortical hormones which in turn causes a fall in the number of eosinophils in the circulation has provided us with a possible test of adrenal efficiency Our own experience of the test has been very limited it appears to have many fallacies but out of it there may well emerge a more acceptable method of detecting the adrenal weakling

Post Operative Necrosis of the Intestinal Mucous Membrane— In 2 patients lethal circulatory failure was due to widespread necrosis of the intestinal mucosa a rare complication of operation

In the first patient a male subject aged 51 partial gastrectomy had been carried out for duodenal ulcer with stenosis The operation itself was not difficult but before it began and immediately after an injection of pentothal the blood pressure which had been 180/120 on the previous evening fell rapidly to 70/60 and remained at a persistently low level throughout the operation and for the succeeding five days before death After the second day there was some abdominal pain and distension and a considerable quantity of extremely offensive brownish fluid was aspirated through an indwelling duodenal tube By the fourth post operative day the abdomen was tympanitic though bowel sounds were audible but the blood pressure remained low and there were signs of peripheral circulatory failure On the day following

overcome it In each case autopsy confirmed the absence of peritonitis or of a mechanical obstruction, each was vigorously treated by gastric suction and by fluid and salt replacement but with no attempt to cater for special electrolyte requirements In retrospect it seems more than likely that the lethal factor was an uncorrected high grade potassium deficiency, and, in extenuation, it is only fair to recall that our appreciation of the importance of potassium is of comparatively recent origin

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deficit which results from the destruction of so many mucosal cells The remarkable recoveries from well managed cholera suggest that early diagnosis and energetic treatment may avert death and allow recovery, at least when the mucosal necrosis has not been beyond repair

This review is a record of our failures It was undertaken primarily for my own instruction and that of my colleagues and it may appear to day to have been too superficial and too discursive It may have focused attention too sharply on the debit side of the surgical balance sheet and neglected on the credit side the encouraging conclusion that when the primary disease is not beyond remedy the patient submitting to operation has better than a fifty to one chance of survival If in the fullness of time the danger of pulmonary embolus can be eliminated the post operative liver deaths prevented and the circulation still more adequately supported in periods of adrenal and metabolic crisis the surgical hazard may well be reduced even further—virtually indeed to that which will remain for ever inseparable from the labours of man s imperfect hand

I must gratefully acknowledge the help and the stimulus of my colleagues Mr A J Slessor Mr C W A Falconer Mr G H D McNaught and Mr J R S Paterson in the preparation of this report which is in fact an account of our united efforts

he lapsed into coma and despite transfusions and stimulants the outcome was fatal

At autopsy the peritoneal cavity was quite free from infection and the peritoneal coat of the intestine was smooth and glistening The small bowel contained a copious amount of offensive fluid, but the most striking feature was the appearance of the mucosa Throughout the small intestine the mucosal surface was more or less completely necrotic, and in part shed There was little or no inflammatory reaction, and the muscle coat was normal The mesenteric vessels showed no signs of obstruction

The second case was also a sequel to gastrectomy this time for a stomal ulcer in a man aged 59 whose general condition on admission was decidedly poor On the second post operative day he passed into acute and severe peripheral circulatory failure and despite resuscitative measures, he died on the third day following operation

The operation itself had been without incident but for a period of about an hour the blood pressure fluctuated between 70 and 90 mm of mercury At autopsy there was again no evidence of intra peritoneal infection, and the anastomosis was satisfactory The jejunum and ileum were uniformly distended but the peritoneal surfaces were smooth and not inflamed When the gut was opened it was obvious that virtually the whole of the mucous membrane of the intestine had been shed exposing the submucosa There was again no evidence of primary vascular damage but histological examination showed an intense necrosis of the mucosa

These cases obviously conformed to a pattern and the clinical behaviour was very reminiscent of Asiatic cholera In both however bacteriological examination failed to demonstrate organisms previously recognised as intestinal pathogens and there was neither peritonitis nor interference with the vascular supply of the small gut

Reports of an essentially similar complication have appeared from time to time during the past twenty years mostly though not invariably after intestinal surgery The absence of any inflammatory reaction and of infection suggests a vascular mechanism as its basis with wide spread curtailment of the blood flow through the mucous membrane There is some evidence that constriction of the mucosal vessels occur in states of shock and in each of the present cases there was certainly a period of hypotension which may have been the precipitating event

Further speculation about its ætiology is outwith the scope of this report It must suffice to record it as one of the rarer complications of surgery but one that it is important to recognise When it has followed surgery elsewhere than in the abdomen the prominent effect is profuse offensive diarrhœa but after abdominal operations diarrhœa may not develop on account of intestinal intubation but there is gross fluid loss by suction The therapeutic indications are obvious therefore for the cause of the fatal circulatory failure is the cataclysmic loss of fluid and electrolytes and in particular the enormous potassium

development of the carpal bones is in contrast normal and the shape of the epiphyses relatively normal The fault is apparently a failure to attain to normal length of bone and is confined to the bones which grow in length by laying down of bone from the epiphyseal plate

A study of the skeleton confirms that the deformities present are all explainable as due to such a fault There is no laying down of abnormal bone, and no persistence of cartilage rests or fibrous tissue within bone as is seen in some of the other dystrophies

A film of the forearm shows that the radius and ulna are shortened and plump with a heavy cortex The proximal end of ulna shows enlargement of the olecranon process The bones of the carpus in contrast are essentially normal

A lateral view of the dorsal spine (Fig 2) shows that the vertebræ are only slightly changed the bodies being of normal size and shape There may be narrowing of the spinal canal in its A P diameter due to a delay or arrest of growth in the vertebral arches In contrast the humerus is short thick and heavy

The pelvis on the other hand shows well marked changes it is flattened with a kidney shaped inlet an acute lumbosacral angle with a protruding sacral promontory and a wide pubic angle These changes again can be explained as due to the altered shape of the individual pelvic bones resulting from an undisturbed periosteal ossification while there is an arrest of ossification from the epiphyseal plate The femur in this film reveals the shortening of the shaft and also a typical shortening of the femoral neck which is in varus position and the relatively large greater trochanter almost reaching to the level of the femoral head

The condition is achondroplasia a congenital growth disturbance in which the essential fault is a retardation or an arrest of growth of the cartilage at the epiphyseal plate leading to a disproportionate dwarfism with marked shortening of the tubular bones of the extremities including the metacarpals and metatarsals Periosteal bone formation proceeds normally The ossification from primary centres in the vertebral bodies and in the small bones of the carpus and tarsus proceeds normally Ossification within the cartilage of the epiphyses is also undisturbed

The opportunity to study another interesting generalised affection of the skeleton arose when a patient a young girl aged 13 years attended complaining of painful lumps in the left hand

Radiographs (Fig 3) reveal that while one hand is normal the affected hand shows in the metaphyses of the metacarpals and phalanges areas where normal bone trabeculation is replaced by homogeneous well defined cyst like translucencies which have apparently originated in bone laid down from the epiphyseal plate and have extended at first endosteally but in other areas through the cortex to present as masses outwith the normal confine of the bones

Here instead of an arrest in growth of bone from the epiphyseal

A REVIEW OF THE RADIOGRAPHIC FEATURES OF SOME GENERAL AFFECTIONS OF THE SKELETON

By Dr W. S. SHEARER

It is obviously impossible to discuss all the general bone dystrophies or diseases which may be encountered, and I do not propose even to present a list of these, but rather to discuss in some detail a few examples and to present each case as it was referred to the X-ray Department, to describe the radiographic appearances, and indicate how a diagnosis was reached. In doing so I hope I may help you in your approach to the study of this subject and I may have some suggestions to make regarding a possible classification or grouping of some general bone dystrophies.

It very frequently happens that examples of general affections of the skeleton, either bone dystrophies or disease, are first manifested clinically as a local lesion which causes symptoms either of deformity or pain. In others the abnormality was first revealed as an incidental finding during radiographic examination for some unrelated condition. In either case an intelligent appreciation of the radiographic findings leads to the suspicion of a generalised skeletal affection and further radiographic examination together with the history and appropriate biochemical investigation enables us to reach a correct diagnosis.

Among the general affections of the skeleton there is a group which can conveniently be classified as those related to abnormality of growth of bone from the epiphyseal plate. I should like to show a few examples of this group.

In December 1948 the Christmas show at the Royal Lyceum Theatre was Snow White and the Seven Dwarfs. One of the dwarfs, Grumpy by name, but a very pleasant intelligent person, had an accident to his hand and came in to the Surgical Out-patient Department. A radiograph of his hands showed an obvious fracture of the first phalanx of the fourth finger on the left side, but in addition there is an alteration in bone structure which is so characteristic that one can hazard a diagnosis on the appearance of the hands alone (Fig. 1). The trident hand with especially pronounced spreading between the 3rd and 4th fingers is evident. The metacarpals and phalanges are abnormally short, they are plump and broadened. The

Read 23rd October 1952

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Here instead of an arrest in growth of bone from the epiphyseal

plate there has been a dysplasia—a fault wherein some tissue other than bone continues to proliferate A radiographic survey of the rest of the skeleton shows the following changes

In the left humerus (Fig 4) on the lateral aspect of the shaft there is an area extending from the epiphyseal plate to the diaphysis where normal bone is replaced by tissue which is partly translucent but alternates with some trabeculated bone and shows an occasional rounded structureless calcified node This mass has extended beyond the cortex into the overlying soft tissues The scapula in this film, and also in an anterior view of the chest shows similar changes involving mainly the vertebral border The demonstration of these changes on an anterior view of the chest emphasises the necessity for examination of the bones in surveying routine chest films

A film of the left femur (Fig 5) shows in the upper end of the shaft on the inner aspect a well defined mass which again has apparently originated endosteally and is expanding to cause pressure erosion of the cortex Smaller areas one of which shows dense calcified nodes are seen lower in the shaft

In the tibia (Fig 5) similar defects are seen and particularly in the lower metaphysis there is an impression of linear columns of translucent tissue extending in from the epiphyseal plate

The left foot shows changes similar to those already seen in the hand while the right foot is normal The condition is an example of dyschondroplasia and the unilateral distribution conforms to the type described by Ollier

Before discussing the nature of this dysplasia may I show films of one other interesting example ? I am indebted to one of my former students Dr P Feltham of Wellington New Zealand for films of the following case which shows a bilateral distribution of the same dysplasia and which reveals in more detail the characteristic radiographic appearances

In both femora (Figs 6 and 7) and to a lesser extent in the tibiæ there is complete loss of normal bone trabeculation and in place of this we see many irregular strands of bone extending from the epiphyseal plate into an expanded metaphysis Between these trabeculæ there are rarefied areas varying in size rounded oval or linear which represent cartilage and scattered rounded or irregular areas of dense opacity which represent nodes of calcification in cartilage These linear columns extending vertically in the metaphysis and the rounded dense opacities scattered within the area are of primary importance in the diagnosis of dyschondroplasia There is a pressure absorption of cortical bone but there is no indication of periosteal reaction or of new bone formation The contrast between this abnormal structure in the metaphyseal area and the normal trabeculation of the epiphysis is striking

A series of films shows the extensive distribution of the disease all four extremities being involved in this case

A study of the radiographs of these two cases with reference to the nature of the abnormal radiographic appearances and their distribution suggests that the condition is essentially a fault in growth of bone affecting mainly the cancellous structure in the region of the metaphyses and involving bone growing from the epiphyseal plate The nature of the fault would appear to be that cartilage fails to develop into bone but remains as columns or irregular masses of translucent tissue Within this cartilage small areas may undergo dystrophic calcification giving a radiographic appearance which is almost diagnostic

The fault appears in early life and as in any fault which has its origin in the epiphyseal plate the abnormal tissue progresses towards the diaphysis with the growth in length of the skeleton It is of interest to note that in the cases seen the fault is most obvious in the rapidly growing portions of the bones

The condition may be polyostotic and show a unilateral distribution as in the first case shown or it may show a more universal distribution as in the second It may in other cases be confined to one limb and almost exclusively monostotic as in the following example

A female patient aged 40 was referred with a history that thirty years previously she had a chondroma removed from the right ankle by the late Sir John Fraser This had resulted in a shortening of the right leg to the extent of half an inch The film (Fig 8) shows that in the metaphyseal areas of the tibia there are bone changes of the type already seen a number of rounded areas of calcification occurring within the expanded metaphysis in association with the defects giving an appearance diagnostic of dyschondroplasia This case might readily be referred to as a chondroma I suggest a more intelligent apprecia tion of the case is to call it a manifestation of dyschondroplasia That this is so was proved by the occurrence of minimal but typical changes of the same type in the femur Radiographs of the rest of the skeleton were essentially negative Similarly the first case might be called one of multiple chondromata The designation polyostotic dyschondroplasia of unilateral type is I suggest preferable

The third condition which I wish to discuss is again related to abnormal growth of bone at the epiphyseo metaphyseal junction namely metaphyseal aclasis or multiple exostoses As in the conditions already shown this hereditary fault results from abnormal growth from the epiphyseal plate In contrast to dyschondroplasia cartilage cells are not displaced into the metaphysis continuing to grow as cartilage but they are displaced laterally and form out growths of cancellous bone from the metaphyseal margins

Although the fault in this dystrophy is again a congenital one and recognisable in early infancy on radiographic examination it is as a rule not recognised clinically until puberty when the greatest growth in length of bone occurs and the exostoses are manifested as palpable lumps sometimes causing pain or limiting mobility of a joint

In other cases the condition is encountered during examination for an unrelated disease Although the metaphyses of the long bones are the commonest site and the site where the appearances can best be studied radiographically, the condition also involves the pelvis scapulæ and ribs and may first be noticed on radiographs of the chest

The case illustrated is such an example A lad of 20 years was referred for a radiograph of the chest with clinical suspicion of tuberculosis The film (Fig 9) showed an area of infiltration which proved to be tuberculous In addition, however the film showed small exostoses related to the vertebral border of the scapula on both sides and involving the anterior ends of the ribs

A film of the knees (Fig 10) shows the typical appearance of metaphyseal aclasis There are seen out growths of cancellous bone covered by a layer of cortical bone extending from the shaft near the epiphyseo metaphyseal junction The cancellous bone of the shaft is continuous with that of the exostoses, and the condition has been aptly described as a protrusion of cancellous bone At the apex of the exostoses there is a cap of cartilage which is not visible radiographically except when it is calcified The cap is covered also by cortical bone The site of insertion or protrusion of the exostoses may present a narrow or broad base As in the case of dyschondroplasia already studied the number and size of those exostoses parallel the rapidity of growth of bone—hence the knee is a convenient area to study In the larger lesions there may be associated deformity of the adjacent bone from pressure erosion and there is usually some alteration in the shape of the metaphysis—a degree of expansion or clubbing due to the underlying fault in growth of bone from the epiphyseal plate This is well illustrated in a film of the pelvis (Fig 11) of this same case and it is well to recall that the presence of even a relatively small exostosis extending into the pelvis may be of serious significance in the female

The exostoses usually cease to grow when the epiphyses fuse but occasionally either the exostosis or more often the cartilage continues to grow as a local chondroma which may exhibit malignant changes to a chondro sarcoma

The radiographic appearances in this condition are so well defined that the problem of differential diagnosis rarely arises The only difficulty might be in relation to a solitary exostosis is this a monostotic manifestation of metaphyseal aclasis or is it a simple tumour? The answer might be given by a careful study of the family pedigree

So far we have seen a condition where the essential fault is a delay or arrest in growth of bone from the epiphyseal plate one where cartilage fails to develop to normal bone but presents as cartilage growing endosteally and one where cartilage cells are displaced from the epiphyseal plate laterally and form bone outside the normal confines of the metaphysis I should like now to show two cases of a disease where the condition is partly due to a laying down of abnormal bone



Fig 1



Fig 2



Fig 3



Fig 4



Fig 5



Fig 6



Fig 7



Fig 8

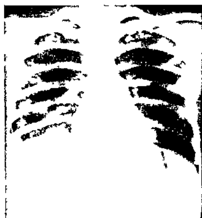


Fig 9



Fig 10



Fig 11



Fig 12

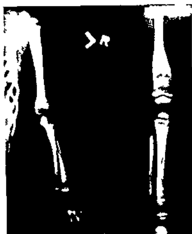


Fig 13



Fig 14



Fig 15



Fig 16



Fig 17



Fig 18



Fig 19



Fig 20



Fig 21



Fig 22



Fig 23



Fig 24

from the epiphyseal plate—osteopetrosis or Albers Schonberg s disease In this rare inherited disease the abnormality is not confined to the bone growing from the epiphyseal plate the condition involves the whole skeleton including the membrane bones of the vault of the skull but in regard to the long bones the distribution of the abnormal bone in relation to the epiphyseal plates is readily demonstrated radio graphically We had the opportunity of studying two cases of this disease the condition occurring in a mother and child and illustrating the hereditary factor

The child when first referred for X ray examination was under the care of Dr John Thomson pædiatrician to the Royal Blind Asylum The child showed a degree of retarded mental development and there was bilateral optic atrophy There was no clinical evidence of hepatomegaly or splenomegaly and examination of the blood did not show evidence of anæmia as frequently manifested in severe forms of this disease Radiographic investigation demonstrated unusually well how the abnormal bone is laid down in layers and also the occurrence of a temporary remission in the disease process

A film of the pelvis and lower limbs at 9 months of age (Fig 12) shows the dense petrosed bone with in the metaphyses alternating bands of dense abnormal bone and relatively normal bone There is a degree of clubbing of the ends of the long bones In the epiphyses and also in the iliac bones of the pelvis the characteristic dense bands are again apparent

A more extensive skeletal survey at the age of 14 months showed (Fig 13) in the limbs that in the intervening period relatively normal bone had been laid down and the dense petrosed bands are now passing towards the diaphysis This temporary remission of the disease is also apparent in the epiphyses and in the metacarpals where the petrosed bone shows as a central density surrounded by bone of normal structure It is of interest to note that the tendency to clubbing of the metaphyses is also less marked during this period when normal bone is being laid down

A lateral view of the spine (Fig 14) shows in each vertebral body a central dense area of petrosed bone surrounded by normal bone This is in contrast to the appearances described in some published cases where the features are a peripheral density surrounding the central normal area Presumably the appearances depend on the phase at which the patient is examined

A further opportunity to examine this patient arose four months later when he developed a fracture of the lower third of radius The films (Fig 15) reveal the straight transverse nature of the fracture apparently occurring through a layer of petrosed bone or at the junction with a normal layer

Unfortunately this patient died shortly afterwards from an inter current infection and we were not given a chance to follow up what would have been a very interesting study

A survey of the skeleton of the mother showed evidence of a diffuse osteopetrosis She was a symptomatic and quite unaware of any abnormality A film of the pelvis (Fig 16) shows petrosed bone with the typical zones or layers parallel to the iliac crests and a degree of expansion of the pubic segments corresponding to the expansion which occurs in the metaphyseal ends of the long bones

DYSFIBROPLASIA

There are many affections of the skeleton, either localised or multiple lesions in which the essential feature is a fibrosis or a fibrous dysplasia where the normal trabeculated bone structure is replaced by fibrous tissue showing a homogeneous appearance on radiographic examination and a varying degree of associated sclerosis and cystic changes These lesions do not show clinically, radiographically or on pathological examination evidence of an inflammatory process and the term osteitis is a misnomer The term dysfibroplasia is a better one and in its widest grouping might be taken to include such local lesions as bone cysts monostotic manifestations of fibrous dysplasia and perhaps giant cell tumours and multiple lesions such as polyostotic fibrous dysplasia hyperparathyroidism and perhaps even Paget s disease of bone

Of this group I should like to show first an example of dysfibroplasia of the polyostotic type which was associated with areas of pigmentation in skin and precocious puberty giving the so called Albright s Syndrome

Although the condition had been present since early childhood it was not manifested clinically until the age of 14 years when the girl developed pain in the left hip with a limp and was referred for examination as a suspected tuberculous disease of the joint The film taken at that time showed normal articular surfaces of the hip joint but there was a marked coxa vara due apparently to a pathological fracture through a cystic area in the neck of the femur Some alteration in the architecture of the shaft was also noted Examination of the skeleton at that time revealed that the condition was part of a generalised affection and a diagnosis of polyostotic fibrous dysplasia was made

The films were taken in 1951 when the patient was 17 years of age The earliest manifestation of dysfibroplasia in these films (Fig 17) is probably best seen in the lower third of the shaft of the left fibula where there is a fusiform area of homogeneous density replacing the normal bone structure This probably started as a small area in the cortex which has slowly increased in size causing pressure erosion and a diffuse expansion In published cases of this condition such early lesions have been noted when they were only a few mms in diameter It should be appreciated that there is no evidence of periosteal reaction as in an inflammatory process In the tibia the appearances are those of a more advanced stage Here there is a

degree of widening of the shaft as a result of the hyperplastic process extending within the medullary canal and there is a degree of sclerosis There is still no evidence of periosteal new bone formation

In the right humerus (Fig 18) in the lower shaft there is again a fusiform area of loss of normal bone trabeculation associated with some local expansion of the cortex and exhibiting at its upper margin a well defined termination which is characteristic In the left humerus the cortical lesions are associated with some sclerosis

It is of fundamental importance to note that the bone structure in the uninvolved areas is essentially normal in contrast to the generalised osteoporosis of hyperparathyroidism

It is well also to contrast the appearances with those of dyschondro plasia with which the condition is sometimes confused The main points of differentiation radiographically are the origin of dyschondro plasia in the cancellous bone of the metaphysis in contrast to involve ment of the cortical bone and the shafts in dysfibroplasia The local lesions in dysfibroplasia show a homogeneous ground glass appear ance with a varying degree of sclerosis or cystic changes in contrast to the trabeculated appearance of dyschondroplasia and the small rounded areas of calcification which are so typical

The left femur (Fig 19) shows a relatively advanced stage of the disease an obvious coxa vara with a healing fracture some cyst like expansion of the bone in the region of the greater trochanter and involvement of the shaft with some sclerosis

A feature of dysfibroplasia is a varying degree of sclerosis associated with the disease In cancellous bone with relatively little resistance to the advancing process there is less tendency to sclerosis and more to cyst formation whereas in cortical bone and particularly in the bones of the base of the skull the outstanding feature is dense sclerosis A lateral view of the skull (Fig 20) in this case showed changes typical of dysfibroplasia These are most marked in the base where there is a dense hypertrophic sclerosis involving both the anterior and middle fossa with dense bone surrounding the pituitary fossa There are also a few small translucencies in the vault in the frontal and parietal areas

In the skull the changes were more marked on the left side though not strictly unilateral and the involvement of the limbs although mainly left sided was not strictly unilateral as in many of the recorded cases of Albright s Syndrome

An opportunity to study the radiographic features of hyperpara thyroidism—a generalised osteitis fibro cystica or I prefer the term a generalised dysfibroplasia with decalcification of the skeleton arose recently in a patient admitted to the Royal Infirmary under the care of Mr Quarry Wood This case a female aged 41 years showed distinctive radiographic findings in the skeleton the renal tract the neck and the mediastinum

In regard to the skeletal changes the tendency has been in the

past to describe the appearances in the advanced stages of this disease but it is important to stress the findings in the early cases since the condition which is due to over activity of the parathyroid glands usually associated with adenoma, responds to the appropriate surgical treatment I would stress this by suggesting that in a patient with localised cystic changes or fibrous dysplasia in bone associated with a degree of decalcification of the skeleton the possibility of an underlying parathyroid adenoma should always be considered and the appropriate clinical radiographic and biochemical investigation carried out

This patient was referred in September 1951 for X ray examination of the right leg with a provisional diagnosis of chronic osteomyelitis The films (Fig 21) revealed two oval areas of bone destruction in the middle third of the shaft of the tibia These showed a well-defined margin with no reactive change in the adjacent bone or periosteum There is also a degree of osteoporosis as evidenced by a thinning of cortical bone and a widening of the trabecular spaces

The appearances did not conform to those of an inflammatory process The radiographic diagnosis at this stage lay between dys-*fibroplasia and tumour of osteolytic type* *Examination of the right* humerus showed a well defined area in the upper part of the shaft having the characteristic appearance of a fibrous dysplasia a similar less well defined area was seen in the right femur On these appearances a diagnosis of hyperparathyroidism was suggested and further examination carried out

The skull (Fig 22) showed a diffuse stippled osteoporosis of the vault an appearance which when once appreciated is so characteristic as to be almost diagnostic of the osteoporosis of hyperparathyroidism The film also shows an advanced calcification of the choroid plexus of the lateral ventricles

Examination of the neck and chest showed a soft tissue mass displacing the trachea forwards and slightly to the left of the mid line at the lower cervical level, and a further mass to the right of the trachea at the level of the second and third dorsal vertebræ The shape of this mass did not conform to enlarged thyroid and it was suggested that it was due to a parathyroid adenoma The ribs and the bones of the shoulder girdle showed evidence of a diffuse osteoporosis

Straight films of the renal areas (Fig 23) showed in addition to evidence of o teoporosis of the spine and pelvis bilateral renal calculi which by their size must be in hydronephrotic kidneys and in virtue of their shape must be in kidneys which have failed to rotate and are at the same level suggesting a congenital fusion of the nature of a horse shoe kidney

On the strength of the radiographic findings alone it was thus possible in this case to make a confident diagnosis of hyperpara thyroidism causing a diffuse generalised skeletal osteoporosis plus dysfibroplasia associated with bilateral renal calculi in a horse shoe kidney and due to a parathyroid adenoma It is not often that a

radiologist is in a position to make such a confident and complete diagnosis

I am indebted to Mr Quarry Wood for further notes of this case Biochemical tests carried out on 11 12 51 gave results which confirmed the diagnosis of hyperparathyroidism The serum calcium at that time was 16 4 mgm per cent On 21 12 51 Mr Quarry Wood operated and removed three parathyroid adenomas the total weight of the parathyroid tumours being 71 gm The post operative progress was satisfactory and subsequent biochemical examination showed for example on 27 12 51 serum calcium of 9 6 mgm per cent Subsequent X ray examination shows similar satisfactory progress A film of the involved leg (Fig 24) taken on 3 10 52 shows that there has been considerable bone regeneration surrounding the local lesion in the tibia and also that the general texture of the bone is approaching normal in contrast to the generalised osteoporosis previously seen

These examples of general affections of the skeleton form as I indicated at the beginning only a small section of a very large group of dystrophies and diseases

May I in conclusion try to draw from these examples some suggestions as to the method you should adopt in the study of radiographs in such cases

If a bone lesion as seen radiographically does not show reactive change in the adjacent bone or periosteum which suggests an inflammatory process or the invasive character of a neoplastic process you should then have in mind the possibility of a dysplasia Study then the localisation is it involving primarily metaphyseal bone or does it as in some conditions outside the group we have studied to day involve only the epiphyses or only the small bones ? Study then the nature of the abnormal process Is it merely an arrest of growth does the appearance suggest a cartilage dysplasia or a fibrous dysplasia ? Then proceed to carry out a survey of the skeleton to show the distribution of the abnormal bone Do not forget to note whether the condition is associated with a generalised osteoporosis or whether bone apart from the involved area is normal Then consider the findings in relation to the full history and clinical examination as well as biochemical blood analysis Having done this I think you will at least make an intelligent approach to the correct diagnosis and will usually reach a satisfactory conclusion

THE CLINICAL AND CYTOLOGICAL INVESTIGATION OF PLEURAL EFFUSION

By R F ROBERTSON M D F R C P E M R C P

By far the commonest type of pleural effusion seen in the wards of a general hospital is the so called post primary tuberculous pleural effusion in the young adult although the commonest it is the type about which I propose to say the least The clinical picture with sudden onset of pleuritic pain followed by toxæmia and the rapid development of clear pleural fluid is usually so typical that no other diagnosis need be considered In the average case, investigation can be limited to a diagnostic aspiration confirming the presence of a clear sterile fluid and the performance of routine B S R and X ray of chest It has always seemed to me that biochemical examination of the fluid and special culture of the fluid for tubercle bacilli are largely a waste of materials in this type of case since whatever the results of such investigations the diagnosis prognosis and treatment remain the same There is however one point concerning the young adult requiring discussion Available evidence suggests that the typical post primary tuberculous effusion occurs some months after a primary tuberculous infection For this reason the primary complex in the lung and hilar glands may be in the process of healing at the time of the effusion and may therefore be an inconspicuous part of the clinical and radiological picture In only 8 of 76 consecutive cases investigated from this point of view was there radiological evidence of a primary complex—in 2 of the 8 both pulmonary and glandular components were visible in the remaining 6 only the glandular component was visible As far as the pulmonary component is concerned spontaneous healing is the rule and no special investigation is required apart from more frequent serial X rays for the early detection of possible local progression As far as the glandular component is concerned spontaneous healing is again the rule although *in theory* trouble may arise from bronchial compression causing pulmonary atelectasis / In the presence of pleural fluid and hilar adenopathy atelectasis should be suspected if there is radiological evidence of mediastinal shift towards the side of the fluid In this event bronchoscopy is probably indicated to investigate the possibility of bronchial obstruction and if present its nature and extent In only 1 of the 8 cases in my series showing a glandular component radiologically was atelectasis suspected and bronchoscopy performed Even then no bronchial obstruction was found It is therefore clear

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that bronchoscopy has only a minor role to play in the investigation of primary tuberculous effusion in the young adult in whom unlike the child with similar enlargement of hilar glands the bronchi are sufficiently large in calibre to withstand a considerable amount of compression without actual occlusion taking place

In older patients—and I have chosen the age of 40 as a convenient dividing line—an apparently primary pleural effusion i e an effusion not due to obvious disease in the lungs heart or elsewhere presents a much greater problem in diagnosis because of the lessening incidence of tuberculosis and the increasing incidence of malignant disease In this connection I would like to emphasise that in older patients primary tuberculous effusion is not so rare as one might think Table I illustrates some statistical information which I have collected during

TABLE I

Age Distribution of 236 Cases of Primary Tuberculous Pleural Effusion

Age (Years)	No. of Cases		Per cent.	
Under 20	1 6		53 4	
20-29	66		28 0	
30 39	20		8 5	
40-49	1	4	5 1	10 1
50 59	5		2 1	
60 69	6		2 5	
70-79	1		0 4	

the past five years and refers to the age distribution of 236 consecutive cases of primary tuberculous effusion observed in the Royal Infirmary of Edinburgh It can be seen that 24 or 10 1 per cent occurred in the over 40 age group During the same period of five years in the midst of numerous cases of obvious malignant disease complicated by effusion I have encountered in the over 40 age group 24 cases of effusion which subsequently proved to be due to malignant disease of the lung or elsewhere but which initially had to be classified as primary in type—i e ætiology unknown

Having thus obtained in this age group two comparable series of cases of equal numbers one series tuberculous and the other malignant I thought that it would be instructive from the point of view of differential diagnosis to analyse certain of the clinical features Table II indicates the help which may be obtained from a study of the temperature chart during the first week in hospital The figures are self explanatory A minor degree of pyrexia is common to both neoplastic and tuberculous patients The 3 neoplastic patients with major pyrexia require further comment 1 proved to have deposits of malignant melanoma in the lungs from an undetermined primary site 2 proved to have bronchial carcinoma and in 1 of those further observation of the temperature chart showed a Pel Ebstein type of

pyrexia Bronchial carcinoma may of course cause pyrexia by virtue of inflammatory complications—pneumonia lung abscess bronchiectasis empyema in those 2 cases however, there was no obvious evidence of such complications Presumably the pyrexia was due to the tumour *per se*

TABLE II

Pleural Effusion in Patients over 40 Years of Age
Pyrexia during First Week in Hospital

Degree of Pyrexia	Ultimate Ætiology	
	Neoplasm (24 Cases)	Tuberculosis (24 Cases)
Nil	18	2
Occasional to 99 F	3	5
Regular to 100 F or over	3	17

In Table III some other important features are compared Typical sharp stabbing pleuritic pain is commonly absent from the history of the malignant case or, when present is a transient phenomenon which the patient may not recall unless he is encouraged to do so

TABLE III

Pleural Effusion in Patients over 40 Years of Age
Some Important Clinical Features

Clinical Feature	Ultimate Ætiology	
	Neoplasm (24 Cases)	Tuberculosis (24 Cases)
Pain—Typical pleuritic	7	17
Boring	*2*	*0*
Aching	1	1
Anginal	1	0
Vague abdominal	1	0
None	*12*	*6*
Hæmoptysis	3	0
Finger clubbing	6	0
Fluid blood stained	10	1
Rapid recurrence of fluid after aspiration	10	0

Possibly this is because the rapid formation of fluid in malignant disease causes early and rapid separation of the parietal and visceral layers of pleura Instead of pleuritic pain the malignant case may have a particularly unpleasant boring pain which goes on most significantly even after the formation of a large effusion this is probably due to invasion of nerves and is never observed in tuberculosis Finger clubbing occurred in 6 malignant cases all of which proved to have a bronchial carcinoma Blood staining of the fluid on initial

aspiration is of course highly suggestive of neoplasm but as is well known may also occur in the occasional case of tuberculosis More important is the rapid recurrence of fluid after aspiration—filling up of the pleural cavity in the space of twenty four hours or less

Apart from the clinical features analysed in the tables reference must be made to the state of health of patients in the few months preceding the pleural episode necessitating admission to hospital With only one exception the tuberculous patients would not admit to any manifestation of ill health leading up as it were to the final illness this patient complained of vague malaise In contrast of the 24 neoplastic patients 19 had complained of ill health of some kind In the bronchial carcinoma group the complaints were of cough dyspnœa on exertion influenza mild pneumonia obscure malaise with slight fever and vague discomfort in the affected side of the chest In the other carcinoma group the main complaint was of weight loss although dyspnœa on exertion easy fatigue and dyspepsia were also mentioned From those details a general principle emerges in the older person as in the young adult primary tuberculous effusion is usually not preceded by a period of ill health forming in this respect a marked contrast to neoplastic effusion

By assessment of those relatively simple clinical points during the patient s first week in a medical ward and by cytological study of the fluid it is usually possible even when the chest X ray is unhelpful to decide whether the weight of evidence favours neoplasm or tuberculosis If neoplasm is favoured further investigation by means of bronchoscopy thoracoscopy and thorascopic biopsy is clearly indicated and so the patient should be transferred to a thoracic surgery unit without delay If tuberculosis is favoured surgical investigation should be withheld or at least delayed Primary tuberculous effusion in the older person is a potentially grave condition probably meriting immediate treatment with modern anti tuberculosis drugs A course of streptomycin and P A S should be instituted and its effect on the clinical state especially the pyrexia observed Response of pyrexia is highly suggestive of a tuberculous ætiology and would justify the future management of the patient as such

I have purposely delayed reference to searching for the tubercle bacillus in this problem type of pleural effusion so that I might avoid over estimating its importance As you know a patient with a primary tuberculous effusion does harbour tubercle bacilli in the fluid and even occasionally in the sputum or gastric juice but such bacilli are so scanty that direct examination fails to reveal them Special culture is therefore required with the disadvantage of at least four weeks delay before the result is known Since in the majority of cases other means of investigation will have solved the diagnostic problem in less than four weeks it may be asked if special search for tubercle bacilli is worth while I think that it is worth while in that a positive

report from the bacteriologist, belated as it is, may provide the diagnosis in a case which has resisted all other methods In this connection I would suggest that if the search for tubercle bacilli is to be made at all it must be made with a thoroughness which will give at least a reasonable percentage of positive results If as is commonly done only one specimen tube of fluid (10 c c) is sent to the bacteriologist for inoculation on to one Lowenstein Jensen slope the percentage positive is only 16 per cent If on the other hand 10 Lowenstein Jensen slopes are inoculated from 10 specimen tubes of fluid the percentage rises to the more reasonable figure of 52 per cent Similar considerations apply to sputum and gastric juice Some workers believe that the biochemist by estimating the glucose and perhaps the chloride content of pleural fluid, can be of more help than the bacteriologist in differentiating malignant and tuberculous disease, my own experience of this means of investigation is limited but suggests that the findings are too variable to be of much assistance

The Mantoux test is also of limited value in older people Needless to say, a positive test—the usual finding—is of no significance while a negative test unless remaining negative on constant repetition does not exclude with certainty an active tuberculous infection

I now come to a problem best illustrated by reference to one particular patient and his X rays This man, aged 46 developed a left pleural effusion following operation for a perforated duodenal ulcer the chest X ray was said to show inflammatory changes in the lungs in addition to the effusion but antibiotic therapy had little effect Diagnostic aspiration revealed a clear serous fluid with protein content of 1 gm per 100 mils E C G showed a myocardial infarction involving the left ventricle and corresponding in age to the date of the operation although at no time had the history or clinical examination suggested this diagnosis Administration of a mercurial diuretic caused rapid reduction in size of the effusion and clearing of the œdematous—not inflammatory—changes in the lungs This case and others similar have led me to believe that a pleural transudate due to left ventricular failure especially when a silent myocardial infarction has occurred may present unusual features It should be remembered that the protein content of a cardiac transudate is not always low probably because protein is added from superimposed inflammatory changes Hence in a puzzling case of effusion whether or not the protein content is low it is worth having an E C G and even more important giving a mercurial diuretic as a therapeutic test

Pleural effusion due to pulmonary infarction is usually small in size When large however it may cause a diagnostic problem because of the close resemblance of many of the features—*e g* hæmoptysis blood staining of fluid—to those of malignant disease especially bronchial carcinoma Further the cytology of infarction fluid is such that a false positive diagnosis of malignancy is made more often

than on any other non malignant fluid It is always helpful in diagnosis to find a venous or cardiac lesion which could be the site of origin for the causative embolus Even in this connection difficulty may arise since thrombo phlebitis of the leg veins may be secondary to malignant disease with effusion In some cases only the satisfactory progress of the patient on anti coagulant therapy will clarify the position

Since the introduction of chemo and antibiotic therapy for bacterial pneumonia a new type of pleural effusion has appeared to trouble the physician from the diagnostic point of view This is the clear sterile post pneumonic effusion which has to some extent replaced the more easily diagnosed frank empyema As far as hospital practice is concerned a patient with this type of effusion is commonly seen for the first time about two weeks after the onset of his illness—*i e* when the general practitioner having administered an adequate course of sulphonamide and/or penicillin is disappointed to find that the dullness in the chest is persisting or increasing and has begun to suspect empyema neoplasm or tuberculosis In such a case having excluded frank empyema by a diagnostic aspiration the physician should keep one simple rule in mind viz a post pneumonic clear effusion cannot be diagnosed with any confidence unless residual signs of lung consolida tion can be elicited at the time of investigation Fortunately from this point of view a post pneumonic effusion is commonly not large enough to obscure radiological evidence of a resolving pneumonia or the coarse crepitations which may well be heard over the affected lobe even when investigation is delayed If no evidence of resolving lung consolidation can be detected clinically or radiologically the effusion should be regarded as tuberculous or malignant until proved otherwise I wish to minimise the importance of the cytology of the fluid in the investigation of this problem for the following reasons a polymorph exudate although commonly found in a post pneumonic effusion may occur in fluids due to other causes conversely a lympho cytic exudate is not uncommon in a post pneumonic effusion

As an introduction to another type of pleurisy with effusion I would like to describe briefly the case of a female patient aged 39 who was first admitted to hospital in February 1948 For the previous eighteen months she had complained of vague aches in numerous joints but ten days before admission had developed an acute left pleurisy with a high temperature which had subsided prior to admission Five days after admission she developed an acute febrile right pleurisy which went on to effusion the fluid being clear and serous sterile on culture and with a lymphocytic exudate She remained in hospital for 7 weeks during which time the effusion slowly absorbed There was nothing in the clinical or radiological picture to suggest a diagnosis other than tuberculous pleurisy with effusion although the history of vague joint pains and the onset with consecutive left and right pleurisy were considered a little unusual The patient was not seen

again until more than a year later She had kept well during that time apart from mild dyspnœa on exertion but had recently developed fever with bilateral pleuritic pain and once again vague pains in the joints Clinical and radiological examination revealed small effusions in both pleural cavities Following readmission to hospital she became seriously ill with a high temperature and eventually died in coma Autopsy showed not as expected miliary tuberculosis but the vascular, renal and cardiac lesions typical of acute disseminated lupus erythematosus This case illustrates that lupus erythematosus may exist and indeed prove fatal in the absence of many of the text book clinical features and more important from our point *of view, that it may begin with a febrile pleurisy progressing to effusion* in a manner identical to a post primary tuberculous pleurisy You will recall that the patient complained of vague joint pains both before and during her episodes of pleurisy Joint pains are common in lupus erythematosus being due to the arthritic part of the disease but they may also occur with a primary tuberculous infection Sheldon and others refer to this phenomenon as tuberculous rheumatism and believe that it is an allergic reaction in the joints There is I think no doubt that tuberculous rheumatism exists but it is extremely rare in the adult Therefore it would seem wise when presented with acute febrile pleurisy and arthralgia in an adult to think of a tuber culous ætiology but at the same time to observe most closely for the other manifestations of disseminated lupus erythematosus

Having mentioned one of the collagen diseases I now come to another—viz rheumatic fever and with it the problem of whether or not there exists the entity of rheumatic pleural effusion In the past five years I have been asked to see only three cases in which this diagnosis had received serious consideration In the first a typical case of rheumatic fever there was marked dullness at the left lung base but a diagnostic tap failed to reveal fluid and it subsequently became clear that the dullness was due to collapse or compression of the left lower lobe secondary to pericarditis In the second also a typical case of rheumatic fever with pericarditis there was dullness at both lung bases bilateral diagnostic aspiration showed fluid with a very low protein content and I have no doubt that the effusions were transudates secondary to cardiac embarrassment In the remaining case the presenting illness was pericarditis with vague joint pains followed in a few weeks by acute pleurisy with effusion a tentative diagnosis of rheumatic pericarditis and rheumatic pleurisy was made but sub sequently the patient developed pulmonary and spinal tuberculosis there is therefore no doubt that both the original pericarditis and the pleurisy were tuberculous in origin and that the joint pains were part of the syndrome of tuberculous rheumatism I would not like to say that rheumatic pleural effusion does not exist but the available evidence suggests that it is a diagnosis which should not be lightly made until the possible fallacies have been excluded At this point it is convenient

to mention erythema nodosum about which the old argument tuberculous versus rheumatic still goes on I do not propose to enter the argument save to say this if erythema nodosum and pleurisy with effusion co exist and occasionally they do the ætiology is tuberculous and not rheumatic

I would like to discuss briefly pleural effusion in relation to those diseases which are commonly grouped under the broad term reticulosis In the first place it should be emphasised that with the notable exception of acute leukæmia which may begin as an acute pleurisy with effusion pleural fluid due to a reticulosis is unlikely to present an ætiological problem since for practical purposes it is a complication occurring late in the course of a previously diagnosed and clinically obvious case Even so it is interesting to note that pleural effusion is rare in lymphosarcoma and Hodgkin s disease but is not uncommon in Brill Symmer s Disease (lymphoid follicular reticulosis) Hence the presence of pleural effusion in a patient with the features of a reticulosis is of some slight help in diagnosing the type of reticulosis

Cytological Investigation

Although cytological examination of pleural fluid may in some cases require the services of a skilled pathologist the clinician should not on this account be deterred from doing a simple cytological study on every case in his own sideroom Ten c c of the fluid prevented from clotting by the addition of 0 5 c c of 3 8 per cent sodium citrate is required On this specimen a total cell count may be done using the same apparatus and technique as for a white blood count but on the whole the actual cell count is of practically no value in differential diagnosis and can therefore be omitted The specimen should be centrifuged at moderate speed for five minutes and the deposit spread thinly on a glass slide and fixed by heat The film of cells so obtained is best stained by Leishman s stain using precisely the same technique as that for a blood film By this simple and rapid procedure, a study can be made of the distribution of polymorphs lymphocytes and serosal cells but I would like to emphasise at this point that a Leishman film is of no value in the recognition of malignant cells which do not stain with sufficient detail to enable them to be differentiated with certainty from serosal cells

Since the original work of Widal and Ravaut in 1900 it has been accepted and taught that in pleural fluid predominant lymphocytes mean tuberculosis predominant polymorphs mean simple inflammation and predominant serosal cells mean a mechanical cause such as malignancy cardiac failure or pulmonary infarction While in a general sense this classical teaching is correct exceptions and mixed cell pictures occur so frequently that in the individual case care should be taken not to draw unjustifiable conclusions Having studied 146

serous pleural fluids of varied ætiology, I have come to the following conclusions —

1 Serosal cells provide, albeit in a limited number of cases the most certain help in diagnosis—

(*a*) a count of over 80 per cent occurred only in neoplastic fluids of which a reasonably high proportion (7 out of 29) showed this finding

(*b*) a count of over 60 per cent occurred only in neoplastic fluids *and transudates*

(*c*) a count of over 50 per cent still occurred mainly in neoplastic fluids and transudates but at this level the presence of a single tuberculous fluid indicated that the critical point had been passed

2 Lymphocytes are of little diagnostic value in the individual case Although a count of over 90 per cent is strongly in favour of tuberculosis the occasional case of neoplasm, transudate and even simple inflammation may fall within this percentage Lowering the figure in a limited manner to 80 per cent brings in an appreciable number of neoplastic fluids

3 Polymorphs require careful interpretation A count of over 90 per cent while favouring simple inflammation, can occasionally occur in tuberculosis In my series a count of over 50 per cent indicated simple inflammation or tuberculosis and did not occur in neoplasm, transudate or infarct It should be kept in mind, however that a bronchial neoplasm may be complicated by simple inflammation of the lung and pleura hence if on other grounds tuberculosis is *considered unlikely a polymorph count of over 50 per cent* can be attributed to simple inflammation with the proviso that there may be a neoplastic background

Pleural Eosinophilia

In any Leishman film of pleural fluid a very occasional eosinophil possibly derived from extravasated blood may be observed but in *rare cases at least 50 per cent of the cells may be eosinophils* This phenomenon is termed pleural eosinophilia In the cytological examination of 253 fluids I have encountered pleural eosinophilia on 8 occasions an incidence of 3 2 per cent Table IV gives essential information about the 8 cases It is observed that in *all* the eosinophil content was over 50 per cent reaching a maximum of 82 per cent in case 5 In no case was there associated eosinophilia in the peripheral blood, a fact suggesting that the pleural eosinophilia was local in origin With regard to ætiology the presence of 3 cases of pulmonary infarction is of great interest and importance but perhaps more significant is the absence of neoplasm and proved tuberculosis It has been suggested in the past that pleural eosinophilia is due to the

presence of blood in the fluid Table IV shows that this cannot be the only explanation

Although I have not personally encountered such a case pleural eosinophilia may be associated with blood eosinophilia in hydatid disease Hodgkin s Disease and the group of conditions known as "eosinophilic lung" Hence from the practical point of view the finding of pleural eosinophilia may help the clinician as follows — If blood eosinophilia co exists with pleural eosinophilia the patient should be investigated for the presence of hydatid disease Hodgkin s Disease and eosinophilic lung (Loeffler s Syndrome Weingarten's Syndrome periarteritis nodosa) If there is no blood eosinophilia

TABLE IV

Pleural Eosinophilia—8 Cases

Case	Ultimate Diagnosis.	Eosinophils per Cent	Blood Eosinophilia.	Fluid Blood-stained
1	Pulmonary infarct	52	No	No
2	Pulmonary infarct	56	No	Yes
3	Pulmonary infarct	55	No	No
4	Traumatic	60	Not done	Yes
5	Pneumonia	82	No	No
6	Pneumonia	70	No	No
7	Simple inflammatory	58	No	No
8	? Tuberculosis	76	No	No

pulmonary infarction trauma to the pleura and pneumonia should be considered in diagnosis (Although for convenience two groups of conditions depending upon the presence or absence of blood eosinophilia have been given it is not suggested that the distinction is absolute) Malignant disease is an improbable diagnosis in the presence of pleural eosinophilia Tuberculosis cannot be excluded as a cause but the available evidence suggests that it should not be readily diagnosed unless other strong evidence is forthcoming

IDENTIFICATION OF MALIGNANT CELLS

In contrast to the simplicity of recognising polymorphs eosinophils and lymphocytes in pleural fluid the identification of malignant cells is a problem which has long taxed the skill of pathologists and the faith of clinicians The crux of the problem lies in the differentiation of the malignant cell from the innocent serosal cell and I have already emphasised that a Leishman film is useless from this point of view Of the various alternative technical and staining methods available I believe that the best is to regard the centrifuged deposit from a specimen of the fluid as a piece of tissue and to treat it pathologically as such by embedding it in paraffin wax cutting sections from the block so obtained and staining the sections in the usual way with hæmatoxylin and eosin The main objection to this method is that

during processing the cells become shrunken and slightly distorted but in my opinion *this is more than compensated for by the clarity* of the picture obtained Further in the course of his ordinary work, the pathologist is accustomed to studying paraffin sections and hence to him the shrunken cell is a normal phenomenon

The following photomicrographs illustrate some of the appearances on hæmatoxylin and eosin sections Non malignant conditions are illustrated first so that a basis for comparison of malignant conditions is obtained

FIG 1 —Pure lymphocytic exudate of tuberculous effusion

FIG 2 —Pure polymorph exudate of empyema

FIG 3 —Mixed picture in tuberculous effusion with lymphocytes polymorphs and occasional serosal cells

FIG 4 —Chronic empyema showing large areas of autolytic cells *it is futile to look for malignant cells in a section of this type*, since they will also show autolytic changes which render identification impossible

FIG 5 —Medium magnification showing the sheets of serosal cells cast off from the pleura following a pulmonary infarction this picture is of particular importance since the aggregations of cells closely simulate the aggregations produced by malignant cells

FIG 6 —Medium magnification from a case of malignant pleural effusion in this instance the aggregations are actually malignant cells, but, at this magnification the resemblance to Fig 7 is obvious

FIG 7 —Effusion secondary to bronchial carcinoma, showing malignant characteristics as follows —

(*a*) *aggregation of cells into a syncytial mass*

(*b*) hyperchromatic nuclei

(*c*) variation in size and shape of cells and nuclei *i e* pleomorphism

(*d*) lack of definition between nucleus and cytoplasm giving the cells a somewhat smudged " appearance

FIG 8 —Effusion secondary to bronchial carcinoma, in addition to a syncytial mass of cells with large hyperchromatic nuclei there is bridging of cytoplasm, or prickles between the individual cells suggesting that the carcinoma is squamous in type (a squamous carcinoma was confirmed by bronchoscopic biopsy) in this section prominent nucleoli are also observed nucleoli may sometimes be observed in innocent serosal cells but innocent nucleoli are never as large as those seen here

FIG 9 —Effusion secondary to bronchial carcinoma there is a large mass of tumour tissue perhaps broken from the surface of the lung by the aspirating needle this is an unusual but helpful occurrence

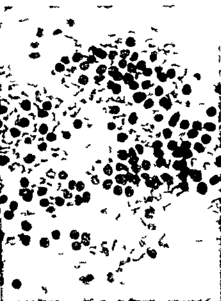


FIG 1 × 600

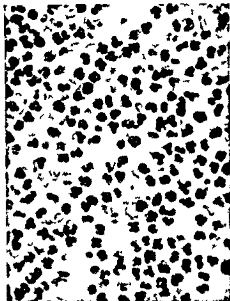


FIG 2 × 600

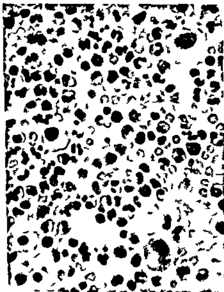


FIG 3 × 600

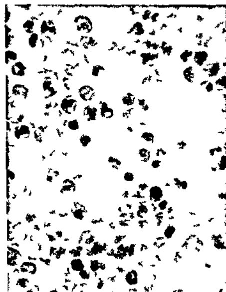


FIG 4 × 600

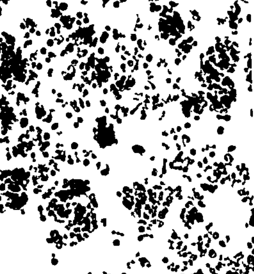
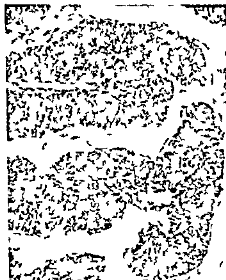

Fig ×150


Fig 6 50


Fig 7 ×600


Fig 8 ×600



Having seen this series of photomicrographs, the clinicians among you must inevitably have one question in mind What is the practical value of cytological diagnosis in malignant pleural effusion? In attempting to answer this question I would like to stress several points —

1 A pleural effusion due to malignant disease does not necessarily contain any malignant cells For example in bronchial carcinoma the fluid may be secondary to lymphatic obstruction in the mediastinum

2 Even if the fluid does contain malignant cells the pathologist may not be able to identify them *positively* as such

3 Because of the influence of those two facts the clinician should not expect too much of the pathologist analysis of my series of cases indicates that only 24 per cent of all malignant effusions can be diagnosed with absolute certainty by cytological examination

4 Although 24 per cent may seem a disappointingly low figure it is still sufficiently high to justify the method of investigation especially as in certain cases it may solve a serious diagno tic problem

5 From another point of view, 24 per cent is a disappointingly high figure since the finding of malignant cells indicates dissemination of the tumour and therefore a bad prognosis Cytological diagnosis is not early diagnosis

No discussion on this topic can avoid reference to error in diagnosis by the pathologist By error in diagnosis I mean the diagnosis of malignancy which does not exist the so called false positive From a special study of the slides of false positive cases occurring in the Royal Infirmary of Edinburgh during the past two years I am convinced that errors occur mainly when the diagnosis has been based on the presence of individual cells thought to have malignant characteristics The risk of error is greatest when the fluid is due to pulmonary infarction or cardiac failure in both of which the serosal cells cast from the pleura may individually resemble malignant cells The typical case of malignant disease with the features I have already demonstrated—viz a syncytial mass of cells with hyperchromatic nuclei pleomorphism smudging and possibly large nucleoli—actually presents no difficulty in diagnosis, and only the typical case should be diagnosed as positive Only by calling the doubtful case negative will the pathologist eventually gain the confidence of his sceptical clinical colleague

The clinician should keep in mind that the preparation of blocks and sections from pleural fluid means a great deal of time consuming work to the technical staff in a busy pathology laboratory and therefore a certain amount of selection should be exercised in the type of fluid sent for examination The selection is best made by study of a simple Leishman film If the cell picture is solidly lymphocytic or polymorphic or if autolysis of cells is taking place as in an empyema there is no point in troubling the pathologist On the other hand the presence of suspicious cells justifies further investigation Finally the

clinician, having decided to send a specimen of fluid to the pathologist should do so as soon as possible after aspiration since degenerative changes rapidly occur in the cells increasing the difficulties of interpretation

In conclusion I would like to thank the Physicians of the Royal Infirmary of Edinburgh for allowing me to investigate patients under their care The cytological studies were carried out in conjunction with the University Department of Pathology the staff of which particularly Dr R F Ogilvie were a constant source of help Lastly I must acknowledge the skill of Mr T C Dodds of the Department of Pathology in preparing the photomicrographs

CARDIOVASCULAR DISTURBANCES IN PARAPLEGICS

By D WHITTERIDGE D M F R S
Professor of Physiology at Edinburgh University

WHEN neurologists were faced by the problems of spinal transection in man during the 1914 18 war, their outlook had been formed by the important work of the Cambridge School of physiologists Langley and Anderson and Elliott on the anatomical organisation of the autonomic system and also by the work of Sherrington on the organisation of reflex behaviour by the spinal cord In addition the work of Sherrington (1898) on spinal transection in the monkey had made clear that the differences between the behaviour of the isolated cord in the rabbit and monkey were much greater than those between monkey and man

It is not therefore surprising that the primary interest of Head and Riddoch (1917) in England and of Andre Thomas (1921) in France was the description of the capabilities of the isolated spinal cord in man the appearance of the mass reflex after withdrawal of the controlling effects of higher centres and the analysis of tho e autonomic activities which seemed to form part of the mass reflex

Little was added between the wars, except for a growing interest in reflexes in man executed by the autonomic system Excessive sweating and the pilomotor reaction had been described by Head and Riddoch and by Andre Thomas respectively but our knowledge of sweating had been extended by L Guttmann (1940) and by List and Pimenta (1944) and of vasoconstrictor mechanisms by Carmichael and his pupils at the National Hospital In particular Carmichael Doupe Harper and McSwiney (1939) had shown that distension of the duodenum in man is followed by vasoconstriction in hands and feet In unpublished work Carmichael had observed that rectal distension could have the same effect (*cf* Carmichael 1950)

During the 1939 45 war a number of paraplegics were collected at a Spinal Injuries Centre at Stoke Mandeville under the care of Dr L Guttmann During the years just after the war little groups of paraplegics found in various hospitals in the country gradually were brought to Stoke Mandeville for treatment and later sent on to Paraplegic Colonies or discharged to their own homes Stoke

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Mandeville has remained their centre for medical treatment and periodic overhaul

If one reads the melancholy accounts of the course, for it can hardly be called treatment of paraplegia in the 1914 18 war it is obvious that the immense improvement which has occurred is due in part to the antibiotics Bed sores and urinary infections are now curable in a matter of weeks In addition however, the great emphasis laid in this country, in the United States and in Canada on physical treatment and exercise has produced physically robust paraplegics previously unknown to medicine (Guttmann 1946) It is not therefore surprising that phenomena seldom seen in semimoribund patients have been most conspicuous and have demanded investigation and treatment

The phenomena to be considered here are related to the impairment of the power of the body to keep the blood pressure steady Although the first to be investigated was the uncontrolled rise in blood pressure induced by peripheral vasoconstriction, the uncontrolled fall in blood pressure produced by tilting the patient is more easily described and analysed The dangers of tilting up a paraplegic patient suddenly were analysed by Jonason (1947) He showed that there is a rapid fall in blood pressure with a rise in pulse rate, and rapid loss of consciousness This is apparently due to simple cerebral anæmia The legs become purple and obviously the normal compensatory vasoconstriction does not occur True fainting with a fall in pulse rate may occasionally occur in paraplegics with high lesions The remarkable finding here is that even in patients with high lesions continued exercise in the upright position leads to a greatly improved regulation of blood pressure The fall in diastolic pressure is less and loss of consciousness is much longer delayed Many factors play a part The tone of blood vessels in the limbs improves patients learn to get up slowly and many drink iced water which puts up the blood pressure slightly It is however difficult to imagine true reflex stabilising mechanisms in the cord and we failed to demonstrate any vasoconstriction in the finger during tilting even when the fingers were kept at heart level This problem is so far unsolved but it is possible that there is an increase in the tone of the blood vessels of the legs

The impairment of temperature regulation depends so largely on cardiovascular mechanisms that it may be dealt with briefly Obviously thermoregulating sweating depends on the number of segments below T_1 left under the control of the higher centres In patients with high lesions thermoregulatory sweating is impaired or completely lost as is the power of losing heat by cutaneous vasodilatation It is not therefore surprising to find very high temperatures in these patients When the bladder is distended we shall see that as well as reflex flexor spasms which liberate heat there may be extensive vasoconstriction over most of the body which reduces heat loss In one of our patients the rectal temperature rose from 37 to 40° C in thirty minutes

in these conditions This rate of rise is so great that there must either have been other sources of heat or the rectal temperature was not that of the whole body This is reminiscent of a curious case of rapid rising and falling of the body temperature reported by Paget in 1885 The patient suffering from a transverse lesion of the cord showed a very sharp rise in temperature beginning shortly after he had com plained of abdominal distension and discomfort When the distension of the bowels was relieved the temperature which had reached 108 109 rapidly fell A peripheral vasoconstriction with flexor spasms might account for the phenomena Paraplegics are of course equally incapable of stopping a fall in body temperature since they can neither shiver nor constrict skin vessels

Dr Guttmann s curiosity was excited in 1944 by the clinical observa tions of flushing in the face when the bladder was distended This occurred in patients with high transections in whom there was no obvious nervous connection between the distended bladder and the flushed face We observed the skin temperature changes and found cooling of the lower part of the body and warming of the face and neck To elucidate the mechanisms involved we measured blood pressure and blood flow in skin (Guttmann and Whitteridge 1947) More recently Cunningham Guttmann Whitteridge and Wyndham (1953) measured blood flow in muscle the heart output using the acetylene method and the venous pressure From the first we looked at the results of bladder distension in patients with transections at all levels

The one common factor in all patients with lesions above the cauda equina and with an isolated but intact spinal cord was a constriction of the blood vessels of the legs when the bladder was distended This involved the vessels of the skin as well as of the calf muscles I think this visceral vasomotor reflex is the fundamental reaction It has been demonstrated by Dr Brian More working in Edinburgh in normal human beings when the pressure in the bladder exceeds 50 mm Hg As mentioned before a similar reaction was demonstrated by Carmichael and co workers to distension of rectum and duodenum and it is probably involved in the cutaneous reactions described by Adams Ray and Norlen (1951) and by Wernøe (1936) There is some evidence that constriction of veins may form part of the same reflex

In patients with lesions at or below T_6 there are only minor disturbances The blood pressure changes very little though the pulse rate may fall considerably The heart output is unchanged Accom panying the vasoconstriction in the legs there is an increased blood flow in the skin of the hands and in the forearm muscles Quantitatively these compensatory changes in flow are not very considerable and we suspect but have not proved that there is an increase in blood flow in the splanchnic region

In our experience there is a sharp distinction between patient with lesions above and below T_6 In patients with high lesions the

same vasoconstriction appears in the legs and probably in the trunk This time however there is no compensatory vasodilatation in the hands but on the contrary the blood flow in the fingers goes down sharply We suspect that there is a decrease in splanchnic flow Certainly there is a sharp rise in blood pressure of 50 150 mm Hg The heart output remains the same or falls slightly There is a sharp rise in venous pressure—in one case of 15 cm water—the heart dilates with increase in the size of the right atrium the pulse slows and extrasystoles and pulsus bigeminus are common

The patient complains of pain first in the chest later in the head and it may reach the occiput and become severe The air way of his nose is blocked and flushing of the neck and red blotches of skin over the angle of the jaw may appear The only other increase in blood flow we have detected is an increase in the forearm blood flow in patients with lesions above C_8 The mechanism of this increased flow is quite obscure It may be a four or five fold increase and is accompanied by obvious warming of the surface of the forearm though the skin remains pale and the vessels of the hand obviously constricted The flushing of the face and neck is also difficult to explain but axon reflexes from distended intracranial vessels may play a part

We suggested in 1947 that the headache was probably due to distension of the intracranial arteries by the raised blood pressure This point has been neatly established by Schumacher and Guthrie (1951) who abolished the headache produced by bladder distension by compressing the carotid arteries by the injection of tetraethyl ammonium chloride and by introducing saline under pressure into the spinal theca

The earliest description of this condition which we have so far found is in a paper by A A Bowlby in 1890 He describes the case of a boy aged 18 admitted to St Bartholomew s Hospital with a fracture dislocation at C_7 T_1 and a clinically complete transection of the cord with a sensory level at T_2 He survived for thirty one weeks After twenty four weeks flexor reflexes had returned The patient says that he has a tingling and pricking sensation over the chest when a catheter is passed and after its passage there is profuse perspiration over head face and neck and the development of a bright red rash which persists for fifteen or twenty minutes At the post mortem examination the membranes were intact but the spinal cord was crushed to pulp

There are a number of significant observations in the paper by Head and Riddoch (1917) but their attention was directed so exclusively to the isolated spinal cord to its reflex capabilities and the conditions for the development of the mass reflex that they do not spare much attention for the behaviour of the upper part of the body They remark of one patient with an incomplete lesion at C_7 Gradually it became apparent that one of the most fruitful causes of these outbursts of sweating was a full bladder He would become gradually

conscious of a fullness in the head and of the increasing moisture of his face

It is interesting that Head and Riddoch point out that the most effective stimulus for excessive sweating from the isolated cord is distension of bladder or intestine The vasoconstriction we have described can scarcely be observed clinically without the use of mechanical devices and is therefore much less conspicuous than the profuse sweating obviou to patient and doctor alike Its effects are only readily detectable when it has involved enough of the vascular bed to cause a rise in blood pressure Nevertheless both excessive sweating and the vasoconstriction are excited by the same stimuli their spread is due to ' unregulated activity of the cord and it would be possible to describe both as a part of a mass reflex involving the autonomic system

One should however avoid such a term It is very doubtful whether Head s mass reflex is in any way a primitive mechanism The degree of linkage between bladder contraction and flexor spasms is much less in our cases than in those described by Head The difference probably lies in the absence of the volleys of pain impulses which constantly reached the cord from extensive bed sores and the scarred bladder common in patients in 1914 18

The only other reference in the earlier literature to flushing and fullness in the head following distension of the bladder comes from Lhermitte who said that he had had an officer patient in the 1914 18 war who said that he always knew when his bladder was full because his face became quite red The phenomena which we have described have been confirmed by Bors (1948) Thompson and Witham (1948) Pollock *et al* (1951) Schumacher and Guthrie (1951) and Bors and French (1952)

Bors and French (1952) confirm these general findings in patients with high lesions but feel that insufficient stress has so far been laid on the question of treatment of the paroxysmal high blood pressure Though these and other authors consider that the raised blood pressure threatens life this is not self evident Most paraplegics are still in the younger age groups and the increases in blood pressure are not higher than those which normally occur in muscular exercise of even moderate severity (Bainbridge 1931) However the headaches and sweating produced by casual distension of the bladder and bowel may be distressing to the patient and in patients described by Thompons and Witham loss of consciousness developed It seems likely that some centres for paraplegics are more successful than others in preventing serious rises of pressure in bladder and bowel If however some surgical relief is needed a satisfactory procedure is posterior rhizotomy Bors and French report good results from cutting posterior roots on both sides below T_9 or T_{10} Anterior rhizotomy is harmful in that it produces an atonic bladder and extensive operations on the sympathetic chain in these patients may be hazardous Most patients

who have only diaphragmatic breathing have a vital capacity between 1 5 and 3 litres (Gilliatt Guttmann and Whitteridge 1948) and are not good risks

In conclusion I should like to stress the opportunities for useful work offered by the analysis of the difficulties of paraplegic patients The " sympathies " between organs of the body have been the subject of speculation by physicians from early times We owe it to one of my most distinguished predecessors Robert Whytt once Professor of the Institutes of Medicine in Edinburgh, that we look for nervous pathways as the principal channel by which one organ may modify the behaviour of another Such reflex actions evoked by pain producing stimuli are singularly difficult to study in the intact human being owing to the emotional complications In paraplegics some of these sympathies ', the action of the bladder on the emptying of the rectum, the action of one part of the upper digestive tract on others can be studied in isolation in human beings not otherwise diseased

Such opportunities and such studies can hardly fail to ameliorate to some extent the lot of paraplegics and to throw light on problems common to all mankind

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SOME RADIOSENSITIVE TUMOURS

By RALSTON PATERSON C B E M D F R C S F F R

From Christie Hospital Manchester

It is now common knowledge that some types of malignant neoplasm are characteristically more sensitive than normal tissues to the action of the ionising radiations This selective sensitivity of certain tumours is indeed the whole basis of radiotherapy As would be expected in this world of infinite variety different tumours have differing sensitivities There is probably a complete spectrum from high radio resistance to ultra sensitivity but at the sensitive end of the spectrum it is found that with few exceptions sensitive growths fall into two definite groups

One of those groups is tumours of *limited* sensitivity They are certainly sensitive in that they can be totally destroyed without corresponding destruction of the normal tissue in which they grow Yet the margin is narrow and the dose of radiation required to produce tumour destruction is relatively high This in practice comes to mean that they can only be cured in somewhat limited volumes Most of the commoner epithelial growths with which we are familiar the carcinomas of the mouth of the skin of the cervix uteri and of the breast are of this nature In the techniques which have been developed to treat them strict attention has had to be paid to the limitation of treatable volume We are not concerned with these tumours here

The second big group of truly sensitive tumours form a nice contrast to the first in that the margin between lethal dose to tumour and tolerance of normal tissue is much wider This high sensitivity has two consequences One is that such tumours are very easy to cure if they happen to be small The other consequence of high sensitivity is that the dose which is sufficient for effective treatment can be given to large segments of the body This is fortunate in that one of the depressing characteristics of most of the sensitive tumours as we shall see is their tendency to spread with extreme rapidity from their primary focus of origin In devising treatment policy this innate tendency toward dissemination at first local but ultimately general has always

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to be taken into account The key to successful treatment becomes in fact, the radiation of impressively large volumes of tissue in continuity

One final comment completes this background Within this group of tumours of high sensitivity there are again two subgroups Some of the radiosensitive neoplasia would appear to be in essence systemic or multifocal in nature from the beginning so that permanent eradication of the disease as a whole seems impossible no matter what one does This group includes Hodgkin s disease, lympho follicular and other reticuloses, and in a different sense the leukæmias These are on any long term view still incurable diseases There are also however, a group of true tumours which are genuinely unifocal in origin Admittedly they have this deplorable capacity for rapid dissemination yet if diagnosed and treated adequately while still reasonably limited in extent they can be cured with a quite remarkable degree of dependability There are many such, nearly all of them rarities some of them indeed the real treasures of any cancerologist s museum When they do turn up they are immensely satisfying to treat if approached correctly

It is this second group of sensitive tumours which is the subject of this paper The trouble with them is that they are numerous so in order to avoid tediousness it seemed to me best to describe three characteristic examples of this type of neoplasm as prototypes The three examples are very different in clinical and pathological type yet they are linked in that they are really radiosensitive and if dealt with even reasonably early they can be cured by radiation in a substantial percentage of cases

For each of these tumours, as I hope I can prove to you a new page has been turned The poor prognosis of even fairly recent text books has now an archaic ring

The three tumours I have in mind are —

The nasopharyngeal radiosensitive tumour
Seminoma of the testis
Medulloblastoma of the cerebellum

The Nasopharyngeal Radiosensitive Tumour

In regard to the nasopharyngeal radiosensitive tumour I am quite aware that in using this title I have deliberately hedged as to its pathology As one justification for doing so let me quote the introduction to a paper on this theme by Meekie Professor of Surgery at Singapore He writes —

The problem of the tumours of the nasopharynx is a fascinating one There is interest in the incidence of the tumours dispute about pathology intriguing problems in interpretation of the clinical manifestations, its therapy is an urgent challenge and there is fierce controversy about the very name by which it shall be known

I can echo Professor Meekie s sigh about nomenclature In my own clinic the following labels have been attached to a series of growths

referred to us and which clinically and radiotherapeutically proved to be of this type —

Lympho epithelioma
Reticulo sarcoma
Lympho sarcoma
Endothelioma,
Transitional cell carcinoma
Anaplastic tumour either squamous cell or reticulo sarcoma
Squamous carcinoma of very primitive type

It is possible that the radiotherapist may be able to shed some light into this darkness of pathological indecision There would appear to be two main types of tumour commonly found in the nasopharynx One behaves as a true epidermal tumour—squamous cell carcinoma The other is this tumour By analogy with the response of epithelial tumours elsewhere in the body the first would be expected to be of limited sensitivity and in fact it proves to be so It is curable only at high dose if strictly limited to the nasopharynx and before secondary lymph node involvement The other tumour is of high sensitivity in the sense in which I defined that term earlier It is curable even when there are solid masses of secondary cervical involvement Once again analogy with the response of tumours elsewhere in the body leads to the conclusion that this growth must be in the nature of a sarcoma of mesoblastic origin in lymphoid endothelial or reticular tissue Perhaps we can take as a final dictum the conclusions of Harvey and Dawson In their debatable tumours series they say of lympho epithelioma —

'We consider that the tumour thus described really covers two types of malignant growth the epidermoid or transitional cell *carcinoma* and the reticulum cell or lympho *sarcoma* '

Clinically tumours of the nasopharynx present in quite a variety of ways because they start in a hidden corner of the human anatomy and first signs or symptoms depend on the particular direction of growth There may be a mass visibly bulging the soft palate forward and with as its dominant symptom nasal obstruction indeed, if there is one characteristic picture of the sensitive tumour it is this kind of smooth rounded mass about the size of a walnut bulging forward one side of the palate and yet with none of the tumour proper visible below the rim of the palate Less often there is an ulcerated growth whose presence is only realised if the nasopharynx is inspected and for this the key symptom is bleeding Alternatively first symptoms may be related to involvement of the cranial nerve through infiltration upwards into the base of the skull Another route of spread is along the Eustacian tube and in going through a batch of cases I was interested to find how very frequently the first symptom in the history was increasing deafness Lastly we must note that in a surprisingly large number of cases the primary growth in the nasopharynx just remains latent signless and symptomless and the first evidence of disease is the

secondary lymph node involvement in the neck Table I gives an analysis of main symptoms in a group of 40 cases

TABLE I

Symptoms in 40 Cases

Enlarged cervical nodes	27
Nasal blockage	20
Pain	18
Deafness	15
Post nasal discharge	10
Epistaxis	9
Cranial or ocular nerve palsies	8

With this variety in symptomatology this disease makes a happy hunting ground for the diagnostic maestro— Have you looked into the nasopharynx young man ? ' The diagnostic key is of course, to look into the nasopharynx—and to take a biopsy A radiograph of the base of the skull, too, is often helpful by showing visible and at times extensive erosion through the skull base I have occasionally seen almost total loss of the whole base right back to the foramen magnum

There is one curious fact about this disease which has always been and remains intriguing It is uncommon relatively speaking in this country and in America It is really common in Singapore and in Hong Kong but in the Chinese element of the population almost exclusively but not among Malay or other non Chinese races Professor Meekie whom I mentioned earlier says that if walking along the street you see a Chinaman with proptosis or cross eyed you would be on a safe bet to spot a nasopharyngeal growth ! As you know two of the commonest cancers in our Western world are those of the stomach and of the breast Yet statistics from Malaya show nasopharynx growths to be nearly as common as stomach cancer and from Hong Kong one and a half times as common as breast cancer In Hong Kong another pretty study was done by Francis Stock which has not yet been fully followed up After the discovery of the nitrogen mustards and urethane as a treatment for the reticuloses a group of these nasopharynx cases was tested on these drugs and a remarkable response to urethane was noted It was not durable unfortunately

We now come to the question of treatment Where the pathology is definite there is no problem The squamous cell carcinomas the other common tumour of this site are dealt with on high dose small volume principles The sensitive tumours have to be approached on the wholly different lines I will indicate in a moment It is where the pathology is indefinite particularly where lymph node involvement is present that doubt arises Such cases have to be given the benefit of the doubt and treated as if sensitive

This is not the place to go into detail of treatment We are here concerned with principles The secret of cure as opposed to temporary

resolution lies in irradiation of large volumes in continuity The neck nodes have to be presumed as involved even if they cannot be felt At the upper end of the treated volume the fields go right up into the base of the brain Some of the most pathetic tragedies of the earlier evolution of this technique were due to recurrence in the gasserian ganglion region with an otherwise apparently cured tumour

Because the volume irradiated is considerable and the mucosa of the pharynx and larynx sensitive a brisk reaction has to be accepted as inevitable There is a period of acute misery towards the end of the course of treatment but it is relatively short Experienced nursing is as usual of enormous help in tiding the patient over this period

Finally, what are the results ? Table II shows the five year survival of all cases treated between 1934 and 1948 which were considered on either histological or clinical grounds to be of this type excluding the definite squamous celled cancers

TABLE II

Radiosensitive Tumours of Nasopharynx

Extent of Disease	Number Treated	Five Year Survival
Limited to nasopharynx	15	60 per cent
With cervical nodes	50	42
Generalised	11	0
	76	40

Even these figures have to be read with in mind that the group analysed because of indefinite histology must include some of the less curable epithelial cancers If there were any way of identifying the sarcoma group alone with certainty the cure rate would I think be even higher

There is of course no alternative surgical treatment

Seminoma Testis

This disease presents very different clinical and histological features but the principle of treatment conforms to the same pattern Let us this time approach the subject the other way round and look at statistics first A review of literature regarding the results of surgical treatment before the days of adequate radiotherapy is very confusing It seems clear however that the overall cure rates at five years ranged from as low as 5 per cent to figures of the order of 20 per cent at the most Even this latter figure was only achieved by the use of the full radical operation by no means a minor undertaking This is a graphic reminder of the real malignant character of this disease Table III shows the improvement possible with modern radiotherapy The overall survival rate even when we include cases with pulmonary

metastases present from the beginning is about 50 per cent If, however, we consider only the earlier group of cases without known metastases, we find a rate of over 75 per cent Clearly a huge change in the prognosis has occurred This change was not of course, brought about instantaneously, there was a transition period The tone of

TABLE III

Seminoma of Testis

Results of All Cases Treated 1934 48

Extent of Disease	Number Treated	Five Year Survival
No demonstrable metastases	99	77 per cent
Abdominal or pulmonary metastases	112	28
	211	51

this transition period is best illustrated by quoting the final paragraph from a long article by Nash and Leddy published in 1943 They then said —

" Rœntgen therapy has assumed a position of primary importance in the management of these tumours and has altered the prognosis from one of hopeless to one of subdued optimism

Seminoma testis and its metastases were in fact found in the earlies days of radiotherapy to be especially radiosensitive Probably the first case reported was that by Beclere (1905)—now nearly fifty years ago Indeed seminoma is probably at the most sensitive extreme of the radio sensitive spectrum I have even seen chest metastases which seemed to improve a little after a series of ordinary diagnostic exposures ! Earlier techniques however though helpful, tended to be too restricted in their application They did not face up fully to the somewhat unusual lymphatic drainage system of the testis determined by its embryonic development and illustrated diagrammatically here Local spread to the inguinal or iliac nodes certainly does occur Much more commonly the first focus of metastatic invasion is in the cœliac axis group of nodes lying right up in the upper abdomen between the kidneys Fig 1 is a composite diagram showing the actual distribution of the metastases in a group of cases There may be some embryological explanation of this curious right sided bias which others have also noted but I cannot think what it is In both we have the dominant cœliac axis distribution This is one of the factors on which treatment policy has to be based

The clinical features of this disease are by the very nature of things essentially simple The primary growth is about as obvious a tumour if looked for as the nasopharyngeal growth was a hidden one Even so it is surprising in going through case histories to find how often

the first sign noticed was not this primary mass but the upper abdominal mass This is more excusable with undescended testes which incidentally, are said to be rather more prone to seminoma than the normal In a few cases such abdominal masses were actually explored surgically before the nature of the disease was realised So there is room even here for the diagnostic maestro to gather kudos One unusual case presented with enlargement of the breasts as the presenting symptom

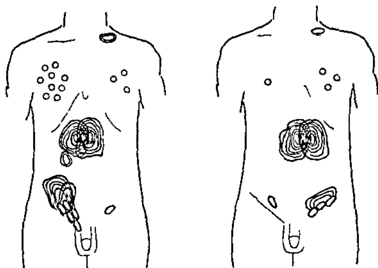


FIG 1 —Composite diagram showing distribution of metastases from seminoma testis in a series of cases primary growths of right and left testicle being shown separately

A characteristic and interesting feature sometimes found is the presence of a positive Aschheim Zondek test Though interesting this test is not a very vital point in initial diagnosis but it can become of value later after the primary growth has been removed as evidence of latent or hidden metastases

Cases of seminoma testis nearly always come to the radiotherapist only after the malignant testicle has been removed and the diagnosis established Histologically seminoma is the commonest of the testicular tumours Two others are important in differential diagnosis and for prognosis—true adenocarcinoma and the mixed element type of malignant teratoma As a general rule we treat both as if they were seminoma To treat a metastatic adenocarcinoma on the same basis as seminoma is really not very rational as it is not sensitive but nothing else is of much use and even pathologists may sometimes be wrong The results are however poor

As indicated the two dominant characters of seminoma testis are its high radiosensitivity and its strong tendency to early intra abdominal metastasis Treatment is therefore indicated in *all* cases even when the primary growth has been removed and no palpable metastatic foci can be felt If this is not done the cœliac axis nodes are apt to

grow to a considerable size before they can be appreciated and then further spread will almost certainly have occurred to mediastinal glands or to the lung For the same reason the treated volume must take in not only the inguinal and iliac fossa region of the involved side but the whole length on both sides of the retroperitoneal area round the abdominal aorta Many radiotherapists approach these as two separate propositions We feel that the needs of the case are more safely met by what is known as " radiation baths to the abdomen

To this particular approach there hangs a sad but fortunately a fairly brief story Some six or seven years ago intent on bettering what was already a good enough technique, had we but realised it, we increased the radiated volume right up to the diaphragm and in one of the techniques even assayed carrying the fields up into the lower mediastinum The kidneys had always been regarded like the liver as relatively radioresistant organs In discovering that they are not so very resistant we ran into a patch of distressing renal damage which gave us great anxiety and led to several tragedies Now we know that a part at least of the kidneys must somehow or other be kept out of the fully radiated treatment zone

The radiated volume is large and treatment has to be prolonged to some five or six weeks to avoid radiation sickness There is also a temporary effect on the hæmopoietic system with a drop in all elements of the white cell count, most marked in lymphocytes

The results of treatment as I have already shown statistically are good The sensitivity is such that an appreciable number of cases can be saved even where large abdominal masses are present Cure is at times occasionally possible even where first abdominal and later pulmonary metastases are found Statistics and general principles are but dry bones To give them flesh here is the story of one actual case

Lieutenant S— age 36 came to us in 1942 from Portsmouth He had a large upper abdominal mass and gave a history of having had a testicular seminoma removed two years before but no radiotherapy The chest was clear He was treated by abdominal baths to a dose of 3000 r over three weeks Two months later our annotation was Fit and well The abdominal mass was gone Six months later the chest was still clear but nine months later multiple tiny metastases were reported and definite supraclavicular nodes felt He was started on chest baths The blood count dropped rather fast and the white cell count fell to 2000 total with 230 lymphocytes Treatment was stopped at a dose of 1650 r Even so four months later our annotation was Remarkably well walks 15 miles while on holiday and now doing full day s work He remains well to day twelve years after starting treatment but clearly he must have had a particularly sensitive growth

Such cases are all very well but nevertheless the real success in this disease is related to the so called prophylactic radiation in cases with no proved metastases But the metastases are there latent just the same

and radiotherapy means the difference between 20 per cent and 75 per cent to 80 per cent survival When one considers that the disease is found in younger rather than older men this curability is quite important

MEDULLOBLASTOMA

Of the three diseases medulloblastoma is certainly the rarest It is in the main a children s tumour and there is always with children a strong emotional satisfaction over cured cases Moreover, it illustrates even more elegantly the treatment principle of irradiation in one undivided volume of a whole potentially invaded area

The initial symptoms are related to its cerebellar origin—ataxia diplopia nystagmus headache vomiting In most instances the cases come to the radiotherapist having been explored and with an histo logical diagnosis ready made Where for some reason or other this has not been possible is it fair to treat on what can only be a presumptive diagnosis ? Even though medulloblastoma is the commonest cerebellar tumour in children every other type of brain tumour can occur in that site On the other hand medulloblastomas are spectacularly sensitive and so in emergency a sensitivity test of X ray therapy to the cere bellum may be used A definitely sensitive response is then followed by radical therapy as in the proved case

The peculiarity of this tumour as compared with most other cerebro spinal growths is that although it commonly starts in the cerebellum it has a wicked habit of metastasising widely and early along the sub arachnoid spaces of the C N S So localised treatment is rendered valueless by new foci in cerebrum or cord Because of this even though its radiosensitive quality was early discovered cure remained rare until it was realised that the whole C N S from calvarium to sacrum had to be radiated At first attempts to do so used a series of contiguous fields The matching edges of the multiple fields gave trouble and lead to a desire to treat the whole C N S in continuity which technically is by no means easy The block of tissue to be radiated is somewhat spade shaped looked at from behind with the brain as the blade and the spine as the handle radiotherapeutically a mo t awkward shape A suitable approach was evolved at the Christie Hospital in Manchester some twelve years ago and simul taneously in Edinburgh and has been gradually improved It has proved a method which yielded rich dividend The basic principle involved is shown in Fig 2 The lateral diagram shows how the X ray tube is taken far enough back to allow the beam to subtend the whole length of the brain and C N S The posterior view shows shaded the extent of the dominant field To equalise dose in the anterior part of the brain additional anterior fields are added to the skull only

What are the results of treatment ? It is I think universally admitted that before the days of X ray therapy medulloblastoma was a 100 per cent lethal tumour and at that a fairly rapidly lethal one

few cases survived over one year Even as recently as 1942 Pendergrass and his colleagues from a first class centre in Philadelphia were prepared to write —

"Possibly trying to cure medulloblastoma is a triumph of hope over reason

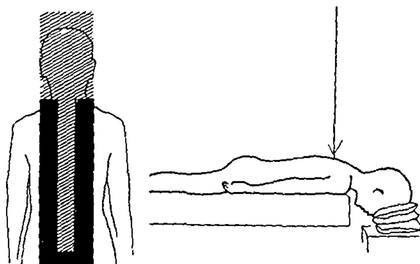


FIG 2 —Diagram showing extent of irradiated zone

The clinical results of present day radiotherapy in terms of function are good Table IV gives the five year statistical results up to date for all cases treated between 1938 and 1948 There is an overall cure rate

TABLE IV

Medulloblastoma

Results of All Cases Treated 1934 48

Number treated	27
Five year survival	44 per cent

of 44 per cent at five years even when all cases however advanced are included This change of prognosis has certain consequences which might usefully be noted

First cure will depend on radiotherapy anyway Therefore no good purpose is served in attempting removal once the diagnosis of medulloblastoma is presumed at operation Indeed apart from decompression and biopsy the less that is done at operation the better Secondly the tumour is so sensitive that there are few cases however advanced which should not be given at least a sporting chance by starting therapy

One other interesting finding may be noted parenthetically It used to be thought that a true nerve tissue tumour such as this would not spread outside the C N S cavity It is only since such cases have

survived for longer periods that more distant metastasis has been shown to be possible and we now have several cases with metastasis to bones

One question may well be asked—what risk is there in irradiating so much brain and nerve tissue in young children ? Intellectual capacity is a difficult thing to measure but it would appear that treatment does not demonstrably lower it One of our earliest cases treated over ten years ago has since taken a full University degree and seems to have performed on a par with his fellows

Note

The medulloblastoma section of the paper was then illustrated by a cinefilm which showed among other things —

(*a*) Cases with the typical ataxia picture

(*b*) The principle of irradiation of the whole C N S in one treated volume

(*c*) The detail of how this was planned to secure homogeneous dosage

(*d*) The actual treatment

(*e*) Illustrative cases including—

(i) One at eight years alive and well

(ii) One at thirteen years alive and having since taken a University degree

Summary

Three tumours are described Each of them are highly malignant growths, apparently of unifocal origin It is claimed that they can be cured in substantial numbers if diagnosed in reasonable time and not necessarily at miraculously early phase These three are illustrative of a larger group of true but somewhat rare tumours of which the same thing could well be said The group includes Wilm s tumour of the kidney neuroblastoma of the sympathetic some tumours of the thyroid gland thymoma dysgerminoma of the ovary and most lympho and reticulo sarcomas wherever found if they are treated before generalisation All of them have the same tendency to rapid dissemination and in all the key to success is the treatment of a relatively large segment of the body In this way radiotherapy has been enabled to make one of its contributions to present day medicine

ANTICOAGULANTS

By CATHERINE C BURT B Sc M B Ch B

From the Department of Clinical Surgery University of Edinburgh

DURING the past fifteen years it has become possible to inhibit or at least to diminish intravascular clotting in patients by the use of anti coagulant drugs This has opened up a large field in the treatment and prevention of thrombo embolic disease

Heparin—a polysaccharide containing glucuronic and sulphuric acid esters—was the first anticoagulant to be used clinically on a large scale by Murray in Canada and by Crafoord in Sweden in the mid 1930s In 1939 40 Link and his associates synthesised dicoumarol 3 3 methylene bis (4 hydroxy coumarin) (Stahmann *et al*, 1941) and in 1948 Reinis and Kubik reported on the clinical use of another coumarin drug an ethyl ester of 4 (hydroxy coumarinyl) acetic acid, known as pelentan or tromexan Reports have also been forthcoming of the clinical use of several other substances chief of which are paritol a synthetic heparinoid substance and phenylindanedione the former being originally reported on by Sorensen and Wright (1950) and the latter by Soulier and Gueger (1947) while at a meeting of the Royal Society of Medicine Walton (1951) reported on the anticoagulant activity of preparations of dextran sulphate The anticoagulant effect of salicylates has also invited some attention but massive doses are usually required to attain a useful prolongation of clotting To date these drugs do not appear to have been used to any great extent for their anticoagulant action but this action should be borne in mind when patients are on dicoumarol or tromexan therapy because salicylates are in common use for minor aches and pains and habitual users seldom think of volunteering the fact The unsuspected use of salicylates may on occasion account for an apparent undue susceptibility to dicoumarol or tromexan

During the last ten years anticoagulant therapy has been employed in Sir James Learmonth s unit in 382 cases The drugs used were heparin dicoumarol or tromexan and I propose therefore to limit discussion in this paper to our experience with these drugs with regard to their action control of dosage difficulties and dangers which have been encountered and to deal briefly with the duration and results of treatment

HEPARIN

Action and Administration—Heparin which acts directly on the clotting mechanism as an antithrombin antithromboplastin and probably antiprothrombin takes effect as soon as it comes in contact

Read 15th May 1952

with blood The anticoagulant potency of the commercial preparations is expressed in international units and solutions of 1000 I U /c c 5000 I U /c c and 25 000 I U /c c are available It can be given by intravenous intramuscular or subcutaneous injection in doses for an adult of from 7500 units up to 12 500 units Within a few minutes after intravenous injection of heparin the clotting time of the blood is pro longed However, the drug is rapidly excreted by the kidneys some of it being fixed in the tissues and three to four hours later the clotting time has usually returned to normal We consider that intravenous injection is the safest method of administering the drug Indwelling needles and polythene tubing have been advocated as a means of avoiding the need of repeated venepunctures When this intermittent intravenous method is used it is advisable to give the drug 4 hourly for the first day or two then as clinical symptoms improve to drop it to 8 hourly then to twice a day and finally to once a day for several days If heparin is stopped too abruptly patients sometimes appear to pass into a phase with an increased tendency to clot In our early cases we estimated the whole blood clotting time before and one hour after each dose but ceased to do this several years ago

Continuous intravenous drip was used only in early cases of our series With this method an initial boosting dose of 5000 units must be given into the drip tubing and thereafter 5000 10 000 units of heparin put in each flask The rate of the drip has to be regulated so that sufficient heparin is given to maintain the clotting time at the desired level which is looked upon as being somewhere in the region of 15 to 20 minutes (Lee and White) This necessitates estimation of clotting times at two to three hourly intervals otherwise there is danger of either over or under dosage

When administered by the intramuscular route the absorption of heparin is slower In our experience following a single dose the maximum clotting time attained is seldom as high as 20 minutes (Lee and White) but it may remain elevated above the control level (5 8 minutes) for periods of 5 or 6 hours However when intra muscular injections are repeated at frequent intervals a depot is gradually built up and we have found that in adults in the post operative state it may be dangerous to continue 4 hourly intramuscular injections of heparin for longer than 24 hours without clotting time estimation Painful hæmatomata are frequently complained of by patients who have been given repeated intramuscular injections of heparin for prolonged periods The extent of bruising which may appear in such cases is illustrated in Fig 1 Loewe and Rosenblatt (1944) advocated the administration of heparin in a pitkin menstruum to slow up the rate of absorption and to give a prolonged action while some workers advocate the administration of 15 000 or even 25 000 units of the con centrated preparation at infrequent intervals, possibly only once in 24 hours In my opinion a depot of this size could be dangerous in the post operative stage

The subcutaneous route has seldom been used because of erratic absorption and the large and visible bruising which appears at the site of injection Tuckman and Moolten (1950) advocated the use of a *subcutaneous depot of hyaluronidase as a means of achieving rapid* absorption of heparin injected into this area We have used this method in a few cases, but the results have been less predictable than with the intravenous and intramuscular routes, although prolongation of the clotting time up to 15 minutes over a period of 2 hours has been achieved The method is moreover not always painless several patients have complained of discomfort at the site of the injection However only moderate bruising has been noted even after four injections in 24 hours

In 1951 Litwins and others reported successful prolongation of the clotting time in a number of patients following the administration of heparin by the sublingual route They stated that in all cases a rise occurred within 30 minutes which reached a maximum in 1 to 2 hours and lasted for from 3 to 7 hours It seemed that if this were so it would be a most useful method of administration and we attempted to repeat their study Sublingual tablets which contained 10 000 units of heparin were obtained and used in 5 cases In one case the clotting time by the Lee and White method rose from 8 minutes to 12 minutes one hour after administration it was 11 minutes 2 hours after and had returned to 8 minutes 3 hours after administration In the 4 other cases given 10 000 or 20,000 units of heparin the clotting time was unaltered *Kennedy and Brown (1952) have recently reported a similar failure* to prolong the blood coagulation time by sublingual administration of heparin

Side Effects—Heparin in itself is a non toxic substance, but idiosyncrasy to it does occur and in 5 of our patients immediately after an intravenous injection there was a complaint of dyspnœa discomfort in the chest a feeling of heat in the head accompanied by flushing and tachycardia The symptoms were transient in all cases but were frightening for both the patient and onlooker In one patient similar symptoms were produced by a subsequent injection and treatment had to be discontinued In the others the intramuscular route was substituted for the intravenous route without further trouble

It has been suggested that heparin may have a vasodilator effect and in a number of our cases ischæmic pain unrelieved by morphine disappeared within a few minutes of the intravenous injection of heparin (Burt 1947) An attempt was therefore made to measure the vasodilator effect if any but plethysmographic recordings of hand blood flow in two subjects before and for one hour after the intravenous injection of heparin failed to show any increase in blood flow However on several occasions rigors and pyrexia have appeared half an hour to an hour after intravenous injection of heparin This reaction was similar to that following intravenous injection of T A B or other foreign protein It seems possible therefore that a moderate vasodilator



FIG 1—The extent of brui ng in the right hip of a patient following four hourly intramuscular injections of heparin for over forty eight hours



FIG 6—Photograph to llustrat petechi l hæmorrhage confined to the aff cted limb n a pat ent with deep venous thrombos who w s on nt coagul nt therapy This patient had had a drip into the s phenous ve n of th s leg wh h had been followed early by thrombosis of the saphenous vein In addition to the pete hial hæmorrhages a hæmatoma formed at the site of the venepuncture

effect might be due to a minor reaction of this type probably caused by protein contaminant in the preparation of heparin

It has been suggested that one of the useful side actions of heparin may be to enhance the fibrinolytic activity of the blood and thus encourage lysis of pre formed clot In 10 cases fibrinolytic activity of the blood was investigated during anticoagulant therapy with heparin In no case was there any evidence to indicate an increase during the period of therapy However Macfarlane and Biggs (1946) have shown that transient fibrinolytic activity occurs in man following psychological and operative trauma exercise and the administration of adrenaline Therefore it would seem that any clot formed during operation or in a period of psychological trauma might contain fibrino lysin We have found *in vitro* that rapid complete lysis of a fibrin clot is dependent upon intimate mixing of the fibrinolysin with the plasma before clotting occurs If the fibrinolysin is added after clotting has occurred only the first 2 or 3 mm of the clot in direct contact with the fibrinolysin becomes lysed in 24 hours From this it would seem possible that clot formed in the immediate post operative period may contain fibrinolysin and thus be less durable than clot formed after the alarm reaction has subsided Rapid lysis of clot may account for the infrequency of thrombotic complications in the immediate post operative period It also seems unlikely that subsequent fibrino lytic activity however induced will materially affect pre formed massive clot in blood vessels However if the clot is spread thinly over a large raw area the whole of this clot might well be removed by subsequent fibrinolytic activity This may explain the excessive hæmorrhage which is feared by most workers when patients are put on anticoagulant therapy following operations such as prostatectomy

Although we have not obtained anv direct experimental evidence of lysis of pre formed clot clinical evidence suggests that provided a thrombus is of recent origin recanalisation is favoured by anticoagulant therapy whether by heparin or by tromexan It may be that this therapy allows a greater degree of natural fibrinolysis to occur by inhibiting further spread of non lysin containing thrombus Fig 2 illustrates the spread of thrombus and recanalisation in the forearm veins in a case of recurrent venous thrombosis Recanalisation occurred in all veins except for 2 cm where the primary thrombosis had occurred It is possible that organisation had already started in this area before anticoagulant therapy was instituted

Antagonists—The action of circulating heparin can be rapidly terminated by the intravenous administration of a 1 per cent solution of protamine sulphate or by toluidine blue We have used only the former clinically and have found it useful in doses of from 1 to 5 c c It will cause a reduction in the clotting time within a few minutes of administration *in vivo* *In vitro* however the effective concentration needed may be about 10 16 times the amount required *in vivo* and has to be determined in each case by the use of serial dilutions of protamine

Concentrations above or below this critical level have an anticoagulant effect and cause further prolongation of clotting time This effect has not been reported to occur *in vivo*

The following case shows the danger of prolonged 4 hourly intra muscular administration of heparin without clotting time estimation as a control and serves to illustrate the need of prolonged transfusion and repeated protamine injection when a heparin depot is present

Fifteen days after total gastrectomy, a male patient aged 55 developed an ileo femoral thrombosis In view of the extensive operation heparin was regarded as the drug of choice, and the patient was put on 10,000 units of heparin intravenously at 4 hourly intervals

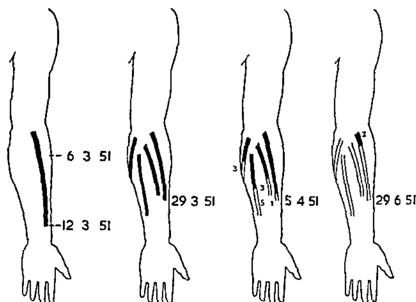


FIG —To illustrate area of thrombo is in superficial veins of forearm and re canalisation Anticoagulant therapy was started after 29 3 51 (Area of thrombosis shown in black measurements in cm)

for 24 hours and thereafter at 6 8 hourly intervals by intramuscular injection His symptoms failed to improve on this dosage and on the twentieth post operative day it was increased to 10 000 units 4 hourly intramuscularly Thirty six hours later large quantities of blood were passed per rectum Heparin was discontinued forthwith but 11 hours after the last injection of heparin he had a large hæmatemesis and passed bright red blood per rectum His blood pressure was unrecordable pulse rate 150 and his clotting time was over one hour (normal 5 8 minutes) He was given 5 c c of protamine sulphate followed by 400 c c of gum saline and four pints of blood This brought his blood pressure to 80/60 mm Hg and his clotting time to 34 minutes A further 5 c c of protamine sulphate were given 12 hours after the first and another pint of blood Six hours later his clotting time was down to 8 minutes and he improved thereafter He was discharged from hospital 18 days after this episode

COUMARINS—ANTI PROTHROMBIN AGENTS

Dicoumarol and Tromexan—These differ from heparin in that their action is not on the clotting mechanism itself but on the inhibition of formation of one of the clotting factors They are both administered by mouth Dicoumarol is prepared in 50 mg tablets and pelentan or tromexan in 300 mg tablets Reinis and Kubik (1948) reported that weight for weight the anticoagulant activity of dicoumarol is approximately four times that of tromexan In our patients the initial dose of dicoumarol used was 200-300 mg on the first day and of pelentan or tromexan 0 9 1 2 g The dosage of both drugs has to be controlled by estimation of the so called prothrombin time which is merely an accelerated plasma clotting time where excess thromboplastin and calcium are added to citrated or oxalated blood A prothrombin time prolonged beyond control levels indicates a low level of prothrombin activity and vice versa There is no absolute normal value for prothrombin time because it depends largely on the potency of the thromboplastin in use Times for normal plasma have been recorded which vary between 10 seconds and 25 seconds and it is necessary to know the range of normal in the thromboplastin which is being used The more potent the thromboplastin the smaller is the rise in clotting time with diminished levels of prothrombin Many workers state that an effective therapeutic dose of dicoumarol or tromexan is attained only when the prothrombin time of the patient under treatment is 2 2½ times that of normal This may be true when a moderately weak thromboplastin is being used that is when the normal time is 16 20 seconds but if the thromboplastin in use gives a normal range of between 10 and 13 seconds then times of 15 25 seconds may be comparable to those of 30 40 seconds given by the weaker thromboplastin

In some laboratories it has been the habit to report on the blood sent for testing by giving a value of prothrombin activity expressed as a percentage of normal This is worked out by the use of dilution curves (Fig 3) We have mainly used Fullerton s method with viper venom for prothrombin time estimation but during the past year have duplicated the tests using in addition Quick s one stage method with brain thromboplastin In general good correlation has been found but as Macfarlane and others have pointed out the use of Quick s method shows a greater rise in clotting time with minor depressions of prothrombin activity than is shown by Fullerton s method and is therefore probably the safer to use We have found however that Fullerton s method gives more consistent results There have been occasions when the clotting times of the same plasma have differed widely with the two methods In one case a female patient aged 38 who had had an acute arterial block had been on anticoagulant therapy for 8 days On the ninth day the viper venom prothrombin time was 14 7 seconds (control 14 seconds) whereas the brain thromboplastin

time was 38 3 seconds (control 12 seconds) As there had been considerable clinical improvement in the condition of her foot it was decided to take the longer time as probably representing the true state of affairs Her dose of tromexan was therefore not increased During the next 24 hours the limb became swollen and the foot gangrenous Further prothrombin time estimations still showed the same short viper venom and long brain thromboplastin times, but whole blood clotting time was normal and amputation was performed without undue

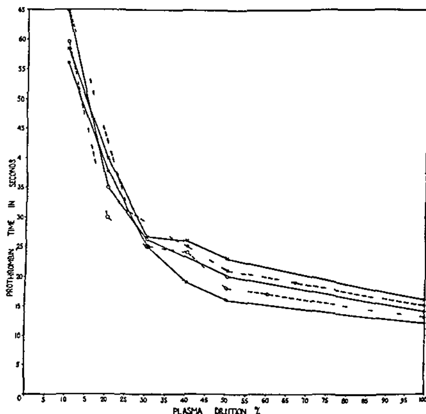


FIG 3—Prothrombin time curves with varied dilutions of plasma in five normal controls using viper venom thromboplastin

bleeding Examination of the amputated limb disclosed widespread recent thrombosis in the calf veins in addition to the old arterial block The reason for the prolonged brain thromboplastin prothrombin time in this case is not known but may have been due to ageing of the thromboplastin which sometimes occurs suddenly In other cases when surprisingly long prothrombin times have been found contamination of the syringe with heparin has been suspected and occasionally proved by protamine titration

For a time it was generally accepted that the prothrombin time of blood was unaffected by the administration of heparin but as was shown by Long *et al* (1946) the prothrombin time may be prolonged immediately after an intravenous dose of heparin It has therefore

been our practice to see that in patients on combined heparin and coumarin therapy blood is withdrawn when the heparin effect is at its minimum that is at least 4 hours after intravenous and 6 hours after the last intramuscular injection When frequent doses of intra muscular heparin are used the patient is continuously under the influence of heparin and quite a large error may be made in prothrombin time estimation and must be allowed for In such cases the true prothrombin time should be determined after addition of appropriate quantities of protamine sulphate or toluidine blue For example in a patient who had been on intramuscular heparin and had been given 1 2 g of tromexan the prothrombin time 24 hours afterwards was 31 seconds this was reduced to 23 seconds by the addition of 0 05 c c of 1/2000 protamine sulphate to 0 1 c c plasma in the clotting system

In our series of cases dicoumarol was used during the first 6 years of the 10 years under review and a typical response is illustrated in Fig 4 The rise in prothrombin time to double the control level is slow and the longest prothrombin times occur several days after the dose has been diminished while the prothrombin time is still elevated well above the control level 5 days after the last dose of 100 mg This initial lag and prolonged action make dicoumarol difficult to control during long term therapy but other workers have reported that good results are obtained by intermittent dosage such as giving the drug on 3 days in the week

In our experience tromexan has proved an easier drug to handle and although as in the case of dicoumarol individual requirements vary widely once they have been established we have found them to remain fairly constant except when systemic upsets occur Fig 5 illustrates the prothrombin activity expressed as a percentage of normal in a patient with deep venous thrombosis of the right leg in whom initial therapy was inadequate and was stopped too early and thrombosis occurred in the left leg 5 days after The first part of the graph also illustrates the disturbance which heparin can cause in prothrombin estimation The initial level of 35 per cent was probably quite erroneous The second part of the graph shows the more typical smooth curve obtained with tromexan alone and also shows the gradual return to normal levels to permit start of massage without danger of bruising

Antagonists —There is no quick way of inhibiting the action of dicoumarol or tromexan and if dangerous bleeding occurs during therapy transfusion with blood is the only way of restoring normal clotting function if severe over dosage has occurred transfusion may have to be repeated daily for some days

Vitamin K in doses of 200 mg or more has been regarded as an antidote to dicoumarol and tromexan but doubt has been thrown on its efficacy in recent publications by Stirling and Hunter (1951) and by Douglas and Brown (1952) who advocate the intravenous or oral use of the analogue vitamin K_1 (2 methyl 3 phytyl 1 4 naphthoquinone)

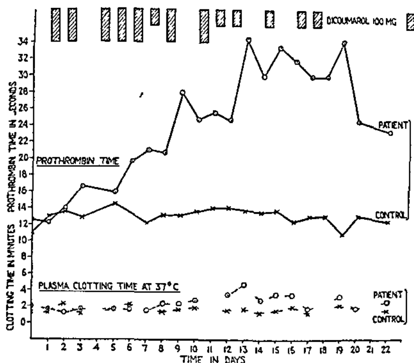


FIG 4—Graph to illustrate control and patient's prothrombin time and plasma clotting time in a case treated with dicoumarol This illustrates the lag in initial rise and the prolonged action of dicoumarol on the prothrombin time and in addition the relatively small change shown in the plasma clotting time

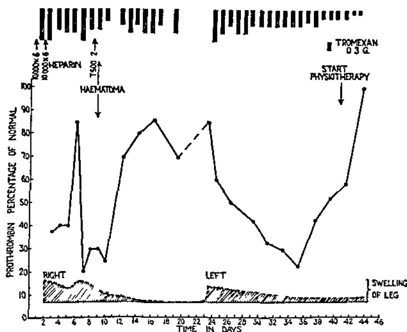


FIG 5—Graph to illustrate the effect of tromexan therapy on the prothrombin activity in a patient with deep venous thrombosis

Out Patient Therapy —Initially we considered that it was unjustifiable to treat any subject as an out patient in view of the danger of over dosage and bleeding from mucous membranes or undue bruising from slight trauma We were forced to change our views by the following case

In September 1948 a male patient aged 48 was admitted to Dr W A Alexander s ward in the Royal Infirmary Edinburgh with a left pulmonary embolus which had occurred one week previously and was accompanied by hæmoptysis Gross swelling and œdema of the left leg were also present Relevant previous history included an attack of pain in the right loin in April 1948 An intravenous pyelogram at that time was negative but the patient stated that for some weeks following this he noticed redness and pain over the veins of the left forearm In June 1948 migratory phlebitis had appeared in the left saphenous territory

He was treated with heparin 10 000 units 4 hourly then 6 hourly dropping to thrice daily and twice daily as clinical improvement was noted Ligature of the left saphenous vein was performed on 28 9 48 under cover of daily doses of heparin 10 000 units On the night of 1 10 48 signs of a left pulmonary embolus appeared and full heparinisation was reinstituted Pelentan was substituted for heparin on 26 10 48 His initial prothrombin time was 12 seconds (control 15 seconds) but after 1 2 g of pelentan for three days this rose to 23 seconds (control 13 seconds) Thereafter a level of between 20 and 40 seconds was maintained on doses of 0 6 g daily with occasionally 0 9 g on a third day Following a course of X ray baths in November to December 1948 he became more sensitive to pelentan and until the end of January 1949 doses of 0 6 g 0 3 g and 0 g in a 3 day cycle were sufficient to maintain the prothrombin time at the previous levels The larger doses then had to be reintroduced

He was allowed home in February 1949 on a maintenance dose of 0 3 g 0 6 g 0 6 g in 3 day cycles with occasional doses of 0 9 g He was readmitted to hospital on several occasions in the following year with signs of over dosage and under dosage For example in July 1949 he had a severe epistaxis when dicoumarol 100 mg daily had been substituted for pelentan during a temporary shortage of the latter drug Several attempts to stop anticoagulant therapy during this year were all followed by an exacerbation of symptoms and spread of thrombosis to the right external jugular vein right leg both arms and on one occasion when therapy had been stopped for one day because of slight hæmaturia a right hemiplegia developed On the following day this responded rapidly to heparinisation and to increase in pelentan In August 1949 suspicion that he had an underlying neoplasm was confirmed by the appearance of nodules in the right posterior triangle of the neck Biopsy of one of these indicated that they were secondary deposits of spheroidal cell carcinoma but no primary site could be suggested Treatment with tromexan was

continued at home and by this time venepuncture had become difficult because so many superficial veins had been previously thrombosed Dosage was therefore regulated by clinical findings and he remained fairly well on tromexan 0 3 g 0 6 g, 0 6 g with occasionally 0 9 g until April 1950 when he had severe pain in the left loin followed by fever and hæmaturia His doctor stopped the anticoagulant therapy justly considering that the hæmaturia was probably due to over dosage but the patient developed a left hemiplegia and died five days later having refused to return to hospital Permission was obtained to perform a limited autopsy at home and the cause of the hæmaturia was found to be thrombosis or embolism of both renal arteries In the right renal artery the block was of recent origin while the left renal artery showed an unusual degree of recanalisation which the pathologist attributed to the action of anticoagulants It is of interest to note that although the patient had for 20 months been on quite large doses of *pelentan* and *tromexan* the liver did not show any gross pathology The site of the primary neoplasm was not found but may have been the thyroid gland which could not be examined

Following this experience we have used long term anticoagulant therapy in a small group of patients with thrombo angiitis obliterans and recurrent phlebitis in whom we thought the risk was justified by the poor prognosis if the condition progressed and at present we are trying it in a small group of patients with arteriosclerosis obliterans The dangers are explained to the patients and their co operation is obtained before start of therapy

Complications —The complications and side effects which occurred under heparin therapy have already been discussed In the patients treated with the coumarin preparations the commonest complication was hæmaturia major episodes of which occurred in 10 cases the majority of these were in cases of operation upon the renal tract Hæmatemesis occurred in 3 patients put on anticoagulant therapy because of post operative venous thrombosis following vagotomy (1 case) and gastrectomy (2 cases) In each case the peptic ulcer bearing area was intact after operation and it is considered that this may well have been the site of hæmorrhage In one patient on dicoumarol a large hæmatoma which caused a transient sciatic nerve palsy occurred following a penicillin injection given when the pro thrombin time was 30 seconds Widespread subcutaneous or petechial hæmorrhages occurred in 5 patients 2 of whom had received prolonged heparin therapy In a third patient it occurred at the site of an urticarial rash, in the fourth following a prolonged period of venous occlusion for a difficult venepuncture and in the fifth was confined to the grossly œdematous and swollen limb for which the patient was receiving therapy (Fig 6) In this patient capillary resistance was normal and her prothrombin time was 27 seconds (control 14 5 seconds) It may be of some interest to record that during the first three days of combined heparin tromexan therapy in a patient who had had a skin graft for a

leg ulcer sero sanguinous fluid secreted in large quantities floated the graft off the surface nevertheless the graft finally took well

Choice of Anticoagulant

In the series under discussion heparin was the anticoagulant of choice in cases where a rapid action was wanted or where it seemed that it might be desirable or necessary to terminate anticoagulant therapy rapidly In 50 cases heparin only was used and heparin was

TREATMENT	TIME AFTER LODGEMENT				
	4 HRS	5 HRS	6 HRS	24 HRS.	11 DAYS
REFLEX HEATING		+	+	+	
HEPARIN-UNITS		10,000 IVI		10000×4 FOR 6 DAYS	
SIGNS					
MUSCLE 1 CONTRACTURE Calf	–	±	±	±	–
2 POWER a) Calf	1	2	3½	4	4
b) Toe flexors	0	0	2	3	4
c) Toe extensors	0	3	3½	4	4
ANKLE JERK	?±	±	+	+	+
PULSE PRESENT + PULSE ABSENT – LEVEL OF 1) ANALGESIA 2) COLDNESS TENDER & TENSE					

Fig 7—To illustrate state of limb and type of treatment in a case of arterial embolism with rapid recovery

also given for the first two or three days in conjunction with dicoumarol (60 cases) and with tromexan (272 cases)

Treatment

(a) *Chronic Obliterative Arterial Disease*—Of the 382 patients reported in this paper 69 were patients with chronic obliterative arterial disease 45 of whom had gangrene or ulceration of toes at the time of admission and 24 had signs of ischæmia of lesser degree Of the 45 who were admitted with gangrene or ulceration 13 improved and were discharged from hospital with their lesions healed or healing after a period of anticoagulant therapy which varied from 2 weeks to 2 months In 29 patients amputation became necessary Three died from progression of their disease

Of the 24 patients without gangrene, 5 progressed to amputation 3 died from progression of the disease soon after anticoagulant therapy had been discontinued Of the other 16 7 improved and 9 are still on out patient long term therapy with tromexan

(*b*) *Acute Arterial Occlusion* —A group of 28 cases of acute arterial occlusion were treated conservatively by anticoagulants and reflex heating Pulses temperature motor and sensory findings were recorded at frequent intervals and if improvement occurred anticoagulant

TREATMENT	TIME IN HOURS AFTER LODGEMENT 5½	7½	8½	10½	13
MORPHINE		GR ¼			OPERATION
REFLEX HEATING	+	+	+	+	
HEPARIN – UNITS	10 000 IVI		10 000 IVI		
SIGNS					
MUSCLE 1 CONTRACTURE					
a) Calf	+	+	+	+	
b) Toe flexors	–	–	–	–	
2 POWER					
a) Calf	5	4	4	4	
b) Toe flexors	0	0	0	0	
c) Toe extensors	4	3½	4	3½	
PULSE PRESENT + PULSE ABSENT – LEVEL OF 1) ANALGESIA 2) COLDNESS					

FIG 8—To illustrate a case of arterial embolism in which the condition of the limb showed initial improvement but later regression under conservative treatment with anticoagulants

therapy was continued (Fig 7) Fifteen of these patients improved and were discharged from hospital In 4 the limb did not improve and amputation became necessary Eight died from the effects of other emboli and one a male aged 60 died from cerebral hæmorrhage at a time when his prothrombin time was 33 seconds against a control of 15 seconds which would be generally regarded as a safe therapeutic level It seems probable however that if a patient develops a small cerebral hæmorrhage while on this therapy the effect of the anti coagulant will be to convert a minor into a major and fatal hæmorrhage and this may have happened in this case

Sixteen cases of arterial embolism were treated by embolectomy followed by anticoagulant therapy within 6 hours of operation Some of these cases were initially treated conservatively but as they had

failed to improve in the first few hours operation was decided upon (Fig 8) In this group 5 recovered Of these 4 had had aortic emboli and one had had a mesenteric embolus Four who had had emboli in the femoral or popliteal vessels lost the affected limbs and 7 died from other embolic episodes

Anticoagulants were given within 6 hours of operation to an additional 15 patients making a total of 31 Troublesome hæmorrhage necessitating cessation of anticoagulant therapy occurred in 5 of these patients and probably contributed to the fatal outcome in a sixth

(*c*) *Deep Venous Thrombosis*—Two hundred cases of deep venous thrombosis have been treated In 140 of these treatment was started within 48 hours of the appearance of signs and symptoms Swelling

TABLE I

Venous Thrombosis

200 Cases

Duration of Signs before Start of Treatment	Limb Swelling				Pulmonary Embolism during Treatment	Died	
	Before Treatment		After Treatment				
	Slight or Absent.	Gross.	Slight or Absent	Gross.		Pulmonary Embolus.	Other Causes.
Under forty-eight hours	67	73	127	13	10	1	2
Over forty-eight hours	9	51	40	20		1†	

One developed a pulmonary embolus following a second operation.

† One died of pulmonary thrombosis one month after anticoagulant treatment was discontinued

was slight or absent in 67 cases gross in 73 Those listed with gross swelling may well have had thrombosis for longer than 48 hours but neither complaint nor signs of abnormality had been recorded In 60 cases symptoms had been present for 48 hours or more before start of anticoagulant therapy

In each case treatment consisted of elevation of the foot of the bed encouragement to move the limbs in bed and anticoagulant therapy—heparin alone in cases which had been recently operated upon or dicoumarol or tromexan covered by an initial 2 days on intravenous and/or intramuscular heparin

A long term follow up has not yet been made but the results at periods from 3 months to 2 years are shown in Table I The course of treatment varied in length from 10 days to 3 months being short in cases where initial limb swelling was slight and early ambulation was possible and prolonged in cases such as an ileo-femoral thrombosis in a patient with a fractured femur where active use of the affected limb was not possible for several months In all cases in which moderate or gross swelling had been noted the affected limb was supported by a crepe bandage or elastic stocking before the patient was allowed to walk

Pulmonary emboli occurred in 10 of these cases during treatment one being fatal This occurred in a man with carcinoma of the colon who had an ileo femoral vein thrombosis *in the left leg He was treated with* 7500 units of heparin 8 hourly by intravenous injection and with physiotherapy He died suddenly on the second day of treatment 15 minutes after physiotherapy and 8 hours after his last dose of heparin I feel that two mistakes were made in this case (1) inadequate heparinisation and (2) an injudiciously early start of physiotherapy

(*d*) *Pulmonary Embolism*—Twenty three patients in whom signs of pulmonary embolism were the first indications of the presence of thrombo embolic disease received anticoagulant therapy In only 8 of these were signs of venous thrombosis in the legs found on examination or evident later Nineteen recovered and 4 died In one of the 4 fatalities a case of suprapubic cystostomy, autopsy was refused but a clinical diagnosis of cerebral hæmorrhage had been made The second patient died of myocardial failure 11 days after the start of anticoagulant therapy, and at autopsy an old embolus was found partially blocking the right pulmonary artery—the pathologist commented upon the absence of secondary clot The third patient was moribund on admission and the fourth died within a few minutes of lodgment of a massive embolus A single dose of heparin had been given immediately after the onset of symptoms

In cases of pulmonary embolism it is probably only where the block is incomplete that anticoagulant therapy can be of value in preventing consecutive thrombosis If the pulmonary trunk or both pulmonary arteries are blocked there is no time for anticoagulants to be of use

In addition to these 23 cases during the 4 years 1947 to 1951 19 fatal cases of unheralded pulmonary embolism have been recorded At autopsy ante mortem thrombus was found in the leg veins in 17 only in one of these had previous pain in the legs been noted In the eighteenth case painless œdema of both legs had been attributed to congestive cardiac failure In only one the nineteenth case was the site of origin of the clot in doubt

(*e*) *Recurrent Venous Thrombosis*—Sixteen patients with recurrent superficial and/or deep venous thrombosis have been treated with anticoagulants In 10 of these patients there was also evidence of obliterative arterial disease There was no evidence of arterial involvement in the remaining 6 patients but they had all suffered several attacks of deep or superficial venous thrombosis or both and 4 of them had also had several pulmonary emboli

The lesions of migratory phlebitis are notoriously erratic in their appearances and disappearances but in the first 2 cases treated with heparin alone for periods of 8 14 days it seemed that the lesions resolved more rapidly than on previous occasions One of these patients did not report back but the other had a recurrence 2 weeks after the first course of heparin and was given heparin again for 4 days during which period

the affected segment of vein recanalised The patient has remained free from attacks of phlebitis for 6 years The condition proved more resistant in the remaining 8 patients who were also treated with dicoumarol or tromexan for periods of 6 weeks to 7 months Fig 9 illustrates the variation in dosage used in one of this group who was treated as an out patient The aim was to keep the prothrombin level about 50 per cent of normal and to prevent a cumulative effect Of the 8 patients so treated 5 have remained free of phlebitis for periods of 2 to 7 years Two in whom arterial involvement was already gross came to amputation and one died following cardiac arrest during a subsequent operation

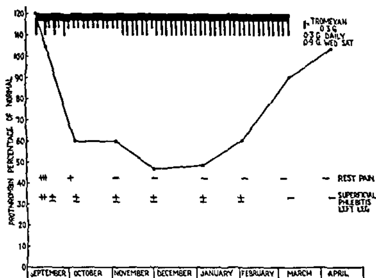


FIG 9—Graph to illustrate the intermittent type of dosage of tromexan and the effect on prothrombin activity in a man with migratory phlebitis treated as an out patient

The 6 patients without evidence of arterial involvement form a somewhat heterogeneous group One of them has already been referred to earlier in this paper as the first patient to be put on anticoagulant therapy as an out patient (p 282) A second whose symptoms closely resemble those of the first patient has been on anticoagulant therapy for two years and each attempt to diminish or stop anticoagulants has been followed by further thrombotic incidents It is suspected that he may have a neoplasm but to date there are no localising signs to indicate a possible site

Although the appearance of spontaneous recurrent deep venous thrombosis may be the first sign of the presence of neoplasm the following case illustrates another possible cause (Fig 10)

A man of 52 was admitted to hospital in August 1949 with spontaneous deep venous thrombosis in the right leg This was treated by full heparinisation and had improved so much in 5 days that we were persuaded to discontinue treatment and allow him to go home In

September and October 1949 he had six minor episodes of right sided chest pain and in October there was a recurrence of venous thrombosis in the right leg, gross swelling and œdema of the leg being preceded by superficial phlebitis in the right thigh, pain in the right side of the chest and hæmoptysis This time he treated himself by rest in bed at home and he improved but swelling of the right leg persisted He came back to hospital in February 1951 with this complaint Dental sepsis was found and tooth extraction advised and this was done under penicillin cover, hæmolytic streptococcus being isolated Before the tooth sockets had healed he had repeated episodes of venous thrombosis in the left forearm When the tooth sockets had healed he was given a 3 months' course of tromexan When seen in March 1952 he was

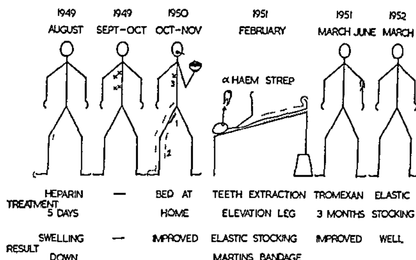


FIG 10 —To illustrate the symptoms clinical findings and treatment in a case of recurrent deep venous thrombosis migratory phlebitis and pulmonary emboli

well It would appear that in this case credit for his recovery is largely due to the dental attention he received and that anticoagulant therapy played a minor part

Of the 3 other patients in this group one has continued to have minor attacks of superficial phlebitis in the lower limbs the other two remained free of symptoms for 6 months and 4 years respectively

(*f*) *Miscellaneous* —I do not propose to discuss details of a small group of patients who were given anticoagulant therapy because of a variety of conditions including one case of frostbite but will just mention that in 5 patients who had had previous thrombo embolic episodes and required operative treatment a trouble free convalescence followed prophylactic anticoagulant therapy given in the immediate post operative period

CONCLUSIONS

In conclusion what did we hope to achieve by the use of anticoagulant therapy in these cases ?

In cases of arterial or venous thrombosis we hoped to prevent or at

least slow down consecutive thrombosis and to permit or encourage resolution of thrombus already present It was also hoped to prevent embolic episodes

It is too early to evaluate the results of treatment in cases of chronic obliterative arterial disease but we have found it is possible to use tromexan for long periods in these cases treated as out patients and it may be that long term prophylactic therapy will prove useful

In cases of arterial emboli in limbs I think anticoagulants have helped to preserve function by preventing consecutive thrombosis and blockage of collateral channels Further embolic episodes have not been prevented

Pulmonary emboli occurred during treatment in 10 of the 200 cases of venous thrombosis being fatal in one This incidence is considerably lower than the 30 per cent reported by Zilliacus (1946) in untreated cases in which the mortality was 9 3 per cent The finding of thrombus in the leg veins of 17 of the 19 patients who died of unheralded pulmonary embolism has made us believe that it should be possible to diminish this number by making greater efforts to discover signs of thrombosis in the limbs at an earlier date

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INFANTILE GASTRO ENTERITIS

By GLENYS M LOWDON M R C P

THE term 'infantile gastro enteritis' has in the past included a group of diseases Some of these have now been recognised as separate entities and it is possible that further distinct conditions may be separated when the ætiological factors are more clearly established I shall first describe the clinical features of the syndrome which is the subject of my lecture

CLINICAL FEATURES

The great majority of cases of non specific gastro enteritis occur in infants under one year of age Over one year of age the occurrence of enteritis is much more frequently associated with a specific intestinal infection

It is important that all enteritis associated with known pathogenic organisms should be excluded such are the shigella group (of which Sonne dysentery is the most common) or the salmonella group (of which aertrycke infection is fairly common) The remaining cases of gastro enteritis are conveniently called non specific' The specific diarrhœal diseases have a known course and some are known to respond rapidly to certain drugs They should not now be included in any study of infantile gastro enteritis unless they are clearly identified

The onset of non specific gastro enteritis is variable Diarrhœa (varying from infrequent but loose stools to frequent copious and watery motions) is present in all cases at some time in the course of the disease Vomiting is not a constant feature sometimes anorexia alone occurs but occasionally vomiting is severe and may be the predominant symptom

The clinical picture apart from diarrhœa and vomiting depends upon the severity of the illness the duration of the symptoms, and the health of the child prior to the onset of enteritis In all but the mildest cases dehydration and electrolyte imbalance are present and in all more severe cases signs of shock and circulatory collapse occur and require active measures for their correction In the most severe cases an infant may be reduced to a dangerous state of circulatory collapse within twenty four hours of the onset of symptoms

The appearance of such an infant is characteristic The eyes are sunken and skin dehydration is present The face and extremities are cold and cyanotic

Autopsy examination of fatal cases reveals nothing except a fatty liver and slight congestion of the gut from which no pathogenic organisms can be cultured

Read 7th June 1951

Fortunately fatal cases are now uncommon except in bad epidemics The disease is so variable that epidemics characterised by cases of quite different severity may occur at different times or in two parts of the country at the same time This variability provides some justification for the view that different ætiological factors may be involved

ÆTIOLOGY

The ætiology of infantile gastro enteritis is not yet understood but various possible ætiological factors deserve attention These may be considered under the following headings—dietetic infections bacterial or virus of the alimentary tract parenteral infections and alimentary toxæmia

With regard to dietetic factors we must first note that it is well established that breast fed babies rarely suffer from gastro enteritis this is probably because they are not exposed to the dangers associated with contaminated milk feeding bottles or teats It may also be important that a breast fed baby is usually better nourished an under nourished infant is more susceptible to enteritis

Apart from these considerations it is not obvious that diet is of ætiological significance Some cases of diarrhœa and vomiting which can be satisfactorily attributed to faulty feeding do occur and should be excluded from the group called acute gastro enteritis This type of diarrhœa is much less common now because of the advice on feeding that is given in welfare clinics and the ready availability of good dried milk preparations

Inevitably the possibility that the disease is due to infection in the intestines has received consideration Many organisms have been suspected of producing gastro enteritis *e g* proteus streptococci type D paracolon bacilli and the toxins of staphylococci The coliform organisms have been incriminated from time to time recent work on certain serological types of *Bact coli* is of interest and will be referred to later

In this connection it is perhaps significant that in cases of non specific gastro enteritis which come to autopsy slight congestion of the gut may be apparent but more frequently no alimentary pathology is found This is in contrast to the pathological lesions of inflammation and ulceration that are found in the intestine of infants with known specific infections such as sonne dysentery This lack of local effect in the gut is put forward as evidence against the infection being due to bacteria within the alimentary tract

The infectivity the lack of immunity and the lack of bacteriological or pathological evidence of infection have led to the suggestion that a virus may be the cause and there is some experimental evidence to support this but this theory also requires further confirmation

The role of parenteral infections in the production of gastro enteritis remains obscure There is agreement that diarrhœa tends to occur

in the presence of some infections among which respiratory infections and otitis media are the most common but a causative relation is not established

An older and rather outmoded theory is that of alimentary toxæmia, it has been suggested that organisms in the gut may, under certain circumstances, produce an excess of tyramine which causes diarrhœa (It is known that the type D streptococcus produces tyramine) This theory does not, however explain the infectious nature of the disease

Gastro enteritis in Edinburgh

With this brief introduction, I propose now to give an account of the trends that have occurred in infantile gastro enteritis in the Royal Hospital for Sick Children, Edinburgh since 1935, and to

TABLE I

Cases of Infantile Gastro Enteritis 1935 1951
Royal Hospital for Sick Children

Year	Total Cases	Total Death	Mortality per Cent
General Wards			
1935 1941	338	119	35
194 1945	308	8	6 6
1946 1947	196	88	44 9
Gastro Enteritis Unit			
1947 1948	158	-	13 1
1949 1951 (March)	375	16	4 3

present a more detailed analysis of the cases that have been treated in recent years in the Gastro enteritis Unit

Prior to 1947, all cases of gastro enteritis admitted to or developing within the wards at the Children s Hospital had to be treated without adequate isolation and this was a constant course of cross infection Fr middle of 1947 a ward was opened at the Edinburgh City he care of cases of non specific gastro enteritis under and later another small isolation ward was made Children s Hospital I refer to these two wards nit"

tedly justified themselves by removing from the general wards and the age of a nursing staff specially

organisms an analysis of cases of gastro enteritis in the Sick and the Gastro enteritis Unit since 1935

The total cases in all years include those admitted with gastro enteritis and those contracting it within hospital You will note the diminishing death rate This is in accord with other published figures For the early years a death rate of 30 to 50 per cent was considered a general average The reduction in mortality in more recent years is largely attributable to the isolation of these cases in special units where treatment has been based on initial starvation followed by graded feeding and perhaps more important the prompt correction of dehydration and electrolyte imbalance by parenteral fluids

There are however other factors perhaps relevant to this fall in death rate which must be considered As has been noted epidemics of varying severity occur from time to time and the mortality is related to the number of severe cases that occur in any period This is well illustrated by the high mortality in the years 1946 to 1947 The most recent severe epidemic of gastro enteritis occurred during this period (actually in the early months of 1947) and of the 196 cases over 70 per cent were of a severe type In contrast in the years before 1946 about 50 per cent and after 1947 about 40 per cent of all cases were severe

The time periods shown in Table I have been chosen because they are related to changes in the routine of treatment 1935 to 1941 represents the pre sulphonamide period During this time fluid replacement was given by subcutaneous intra fontanelle and intra peritoneal routes Many of the infants received no drugs while others had bismuth kaolin castor oil or bacteriophage

From 1942 to 1945 fluid replacement was by the same techniques Sulphaguanidine was used extensively and may have been partly responsible for the fall in death rate

In 1946 to 1947 fluid replacement was usually made by infusions into limb veins Sulphaguanidine was largely replaced by the soluble sulphonamides but on the whole sulphonamides were less constantly used than in the previous period and many cases had no drug treat ment Penicillin injections were given to a few cases

The Gastro enteritis Ward at the City Hospital was started in the latter part of 1947 and the cases treated there are included with 1948 in the next group I have separated 1947 48 from 1949 51 in order to show the recent fall of mortality This has occurred in spite of a slight increase in the proportion of severe cases and is attributable to more strict barrier nursing earlier discharge of the patients to prevent cross infection more efficient fluid and electrolyte replacement and perhaps in part to more prompt and more adequate use of drugs

Since 1947 in the Gastro enteritis Unit fluids have been given intravenously when parenteral replacement was considered necessary In the period since 1949 controlled trials have been made of treatment with sulphadiazine oral polymyxin oral streptomycin and chlor amphenicol Penicillin by intramuscular injection has been used only for incidental staphylococcal infections and otitis media A

detailed analysis of the patients in this last group will serve to illustrate some features of the disease and to show the results of our trials of antibiotic drugs, and of our bacteriological investigation

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Fig 1 shows the age distribution of our cases and will serve to remind you that most cases occur under six months of age with the highest number usually at three months The highest death rate *also occurs in the early months*

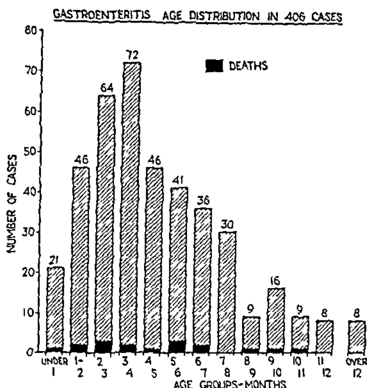


FIG 1

I have mentioned the low incidence of gastro enteritis among breast fed infants in this series less than 3 per cent of cases had been breast fed immediately prior to admission in spite of the fact that most of the admissions are during the breast feeding months of age Another well known feature of the disease is its association with poor social *conditions and overcrowding* This is fully borne out in *our experience* Two thirds of the patients came from their own homes which were with few exceptions overcrowded and unhealthy Indeed a relatively high proportion of these cases came from temporary hutted accommodation The other common sources of patients (which accounted for the remaining third of our cases) are residential nurseries *for* babies and hospital wards The disease is very infectious and the

admission of one patient with gastro-enteritis to an institution or ward is very liable to lead to cross infection As in homes, overcrowding in general wards increases the danger

The seasonal incidence of our cases shows a slightly higher admission rate in the winter months Gastro enteritis used to be called summer diarrhœa simply because the highest number of cases then occurred in the summer months but it has been a general experience in more recent years that this is no longer the case This alteration in the seasonal incidence has led to the suggestion that summer diarrhœa was a different disease

Table II shows the number of infants in whom parenteral infections were present on admission Though the number of patients with oral thrush is shown I have not included these in the total and in the calculated incidence of infections as its presence in these patients was thought to be secondary to the gastro enteritis

TABLE II

Parenteral Infections on Admission in 375 Cases of Infantile Gastro enteritis

Total Cases 375	Respiratory	38	77 = 20%
	Otitis Media	8	
	Skin Sepsis	11	
	Thrush	34	

The finding of parenteral infections in only 20 per cent of these cases is much lower than that reported in many other series but it is of interest that most of the cases with respiratory infection occurred in association with mild epidemics of gastro enteritis in the winter months of 1950 and 1951 Most of the patients in these epidemics either had a respiratory infection on admission or had just recovered from one The significance of this observation is however doubtful because many of these cases came from open general wards where the high rate of admission for respiratory disease had led to overcrowding

The clinical incidence of otitis media is not easy to assess because the diagnosis of this condition is notoriously difficult in infants with gastro enteritis this difficulty is probably the greater because the chemotherapy now used tends further to mask the clinical features of the aural condition It is significant that in the 26 fatal cases since 1946 in which autopsies have been obtained and the ears examined infection of the middle ear and mastoid has been found in 9 or about one third of the cases Prior to the period when antibiotics were available the incidence of middle ear and mastoid infection in 141 cases coming to autopsy was 45 per cent While it is not suggested that the otitis media is a cause of gastro enteritis these observations serve to emphasise that the physician treating this disease must be on the watch for infection of the middle ear particularly in any patient who is not responding to treatment as might be expected

The group covered by the term ' sepsis includes purulent conjunctivitis paronchyia staphylococcal skin lesions and one case of vaccinia with secondary infection These various conditions are probably coincidental

TREATMENT

Before we consider the results of antibiotic therapy in gastro enteritis it must be emphasised that the value of these drugs is still in question and that *the essential treatment is still based on nursing* diet, and fluid and electrolyte control

It has been our practice since the gastro enteritis unit began in 1947 to follow a basic routine in all cases so that the value of any added therapy can be more easily assessed

All cases except the most severely collapsed receive a gastric lavage on admission and in the milder cases this opportunity is taken to leave an appropriate amount of fluid in the stomach for more rapid rehydration One of the dangers in the severely ill child is that of aspiration of vomitus which if it occurs is almost invariably fatal Gastric lavage reduces the risk of this complication as does also starvation

For the first twenty four to thirty six hours after admission all milk is withheld and only water glucose and electrolytes are given—whether these are given by the oral or intravenous route depends on the assessment of the severity of the condition and dehydration on admission

I would stress the importance of a careful clinical assessment at this time All severely dehydrated collapsed or toxic infants require intravenous therapy immediately and in these only the necessary drugs are given by mouth In infants judged to be less seriously ill fluids are given orally the child must then be watched carefully for the first twenty four hours and if there is any intolerance of oral fluids as shown by vomiting or more copious diarrhœa intravenous therapy must be substituted I think it is the better recognition of these danger signs and the *prompt use of intravenous fluid when necessary which has* helped most to reduce the death rate from gastro enteritis The M R C has advised that all cases requiring intravenous therapy within the first twenty four hours should be classified as severe , the remainder as mild and we have used this classification in all our cases

The fluid requirements are based on the formula 2½ oz fluid/lb body weight/day with an initial 10 20 per cent increase to combat dehydration We use half strength Hartman s solution with 5 per cent glucose orally or intravenously in the first twenty four to thirty six hours In all severely collapsed infants some intravenous plasma is substituted for part of the calculated fluid intake

In a few cases signs of severe acidosis appear and it is necessary to correct this by special fluids such as 1/6 molar lactate

Darrow in 1946 demonstrated that infants suffering from diarrhœa and vomiting have an excessive loss of potassium salts and that some die from potassium deficiency In view of this all our cases since 1947, after initial correction of dehydration have received ½-1 gm daily of potassium chloride by mouth or intravenously until adequate milk feeds could be given

Following the initial starvation period graded feeding with milk of low fat content is given for this we use a half cream dried milk. Supplements of vitamins B and C are given from the onset and vitamin K is given in any severe case where liver damage is suspected This regime is usually sufficient but in a few severe cases the addition of blood or plasma by intravenous infusion is beneficial

It remains to consider specific drug therapy In assessing the results of specific therapy there is considerable difficulty in the choice of criteria The mortality rate is now so low that it is of little value in the assessment of treatment A fairly satisfactory solution to this difficulty is to take two figures in each case—the number of days of diarrhœa after admission and the number of days to full clinical recovery when full feeds are tolerated and the infant is gaining weight These criteria have been adopted for the M R C trials

The varying severity of the disease has already been emphasised and for this reason it is essential that any series of cases treated by a drug under trial must be compared with a control series consisting of cases occurring in the same centre at the same time and with cases of comparable age and severity In practice we allocate alternate mild cases and alternate severe cases to the control and trial groups Most gastro enteritis units have treated their control cases without any routine chemotherapy but I have not felt justified in withholding all drugs and we have compared the cases receiving the oral antibiotics —polymyxin streptomycin and chloramphenicol—with cases receiving sulphadiazine This has the advantage that it tends to eliminate the possible fallacy that the antibiotics may be given credit for benefit which is not specific but due to control of incidental or secondary septic infection

Results of Treatment

It is not practicable at the moment to present all the results with appropriate control series and I shall confine myself to showing you a summary of the results of treatment in the last 385 cases

Table III shows the total number of cases in each group and the average number of days of diarrhœa and days to full clinical recovery The relapses and deaths are presented as percentages because the absolute numbers would appear misleading

The 54 cases treated without chemotherapy were early cases and were mostly mild in type This detracts from the value of the figures shown for this group

Parenteral penicillin was given to some patients in each group to treat infective complications such as phlebitis from intravenous

infusions or otitis media but it is not thought to have had any effect on the enteritis and is not represented except in the group of 41 cases in which it was given from the time of admission along with sulpha diazine *The figures suggest that it does not influence the course of* the disease

It will be seen that there is little difference between the results with sulphadiazine and those with chloramphenicol Polymyxin and oral streptomycin appear—judging by the number of days to full clinical recovery—to be less effective

My own opinion would be that these results are inconclusive The relative values of chloramphenicol and sulphadiazine will not be adequately assessed until a severe epidemic of gastro enteritis occurs Other workers have had a more favourable impression of chloram phenicol but it is not possible to say yet whether it has any specific action on gastro enteritis or is merely effective in combating secondary infections

TABLE III

Results of Treatment in 385 Cases of Infantile Gastro enteritis

	T tal N C	A g D y D arrhœa	A g D ys to Cl R	P R lap g	P ent M rt l y
No drugs	54	5 8	19 9	3 7	3 7
Sulphadiazine	158	5 5	1/	3 2	4 4
Sulphadiazine and penicillin	41	5 4	18 7	7 3	4 9
Polymyxin	15	6 3	25 1	0 0	6 7
Streptomycin *(Oral)*	-9	6 5	6 8	3 4	3 4
Chloramphenicol	88	6 3	16 6	7 9	4 5

The dose of sulphadiazine used has been 1 5 3 gm daily for 7 days One case developed hæmaturia and sulphadiazine had to be stopped Otherwise no toxic effects occurred Polymyxin was given orally in a dose of 12 mgm /lb body weight per day for six to twelve days There were no toxic effects Oral streptomycin was given in a dose of 1 2 gm /day for six to twelve days with no toxic effects Chloram phenicol was at first used in a dose of 50 mgm /lb body weight per day for seven days and later 75 mgm /lb body weight per day was given Few toxic effects were noted In some the buttocks became excoriated and skin rashes occurred in a few but these lesions cleared quickly It was noted occasionally that a certain looseness of the stools continued while the infant was on chloramphenicol and this stopped after the drug was discontinued In only one patient did chloramphenicol produce vomiting

Streptomycin produces complete sterility of the stool for a time in many cases the effect of polymyxin chloramphenicol and sulpha tazine is not so complete but there is considerable reduction in the flora Oral streptomycin has however the disadvantages that no systemic antibiotic effect is obtained and that its use tends to produce resistant strains of organisms

BACTERIOLOGICAL STUDIES

In conclusion I would like to refer briefly to our bacteriological investigations In recent years considerable interest has been shown in the relationship of certain serological types of *Bact coli* to gastro enteritis Bray (1945) reported cases from which he recovered a strain which he called *Bact coli neapolitanum* Smith in Aberdeen, has isolated from cases with gastro enteritis two types of *Bact coli* which he called alpha and beta the alpha strain corresponds to Bray s *Bact coli neapolitanum*

In an outbreak in Aberdeen Giles Sangster and Smith (1948 1949) found this alpha strain in over 90 per cent of cases More recently Taylor Powell and Wright (1949) and other workers have found a high incidence of this type of *Bact coli* in epidemics of gastro enteritis It would appear from the work that is at present being

TABLE IV

Incidence of Serological Types of Bact coli *on Admission in 304 Cases of Infantile Gastro enteritis*

	T tal T t d	α (O)	β (O 55)	N g	P t Pos	Per ce t P t S er Cas
1949	90	40	/	50	44	64
1950 (Jan May)	9	69	/	25	75	85
June 1950 to Mar 1951	12	18	74	80	34	43

done that other serological types of *Bact coli* may be associated with clinical gastro enteritis the predominant type varying from time to time and from epidemic to epidemic Unfortunately some confusion in nomenclature has arisen, as several groups of workers have named for themselves strains which have eventually proved to be the same The tendency now is to accept Kaufman s numbering of the types By this classification alpha becomes O 111 and beta becomes O 55 I am going to refer to the two strains (alpha and beta) in the same way as Dr Smith of Aberdeen from whom we originally got our testing sera

I am greatly indebted to Dr Margaret McNeil who has made detailed bacteriological studies on our cases The serological types of *Bact coli* in the stools of most of the infants have been identified and in many these observations were made daily for the whole time the infants were in hospital The typing is based on slide and tube agglutination with specific sera and biochemical reactions

Table IV shows the incidence of the relevant serological types of *Bact coli* at the time of admission From 1949 to May 1950 only the alpha strain was tested for routinely After June 1950 all cases were tested for both alpha and beta strains

Before asking you to accept the significance of these figures, I would like to draw your attention to other observations In the first place, the incidence is higher in the cases which were clinically severe in 1949, 64 per cent and in January to May 1950 85 per cent of severe cases were positive for the " alpha " strain From June 1950 to March 1951, 43 per cent of severe cases were positive for alpha ' or ' beta strains

Moreover these strains of *Bact coli* are not often found in healthy infants No instance of alpha " strain of *Bact coli* was found in 124 infants in nurseries in the town by tests made in the same period

Of 105 infants with gastro enteritis whose stools were positive for alpha " strain on admission 89 (or 85 per cent) had no " alpha *Bact coli* at the time of discharge from hospital

Nor can the appearance of these strains be attributable only to illness or diarrhœa We have found that among 47 infants under two years of age with specific enteritis, only about 19 per cent had the alpha " strain of *Bact coli* in the stool on admission

If we return now to the figures shown for the incidence of the special serological types in infants with non specific gastro enteritis you will note the high percentage of cases positive for alpha ' strain in the first five months of 1950 It is of interest that many of these cases were admitted from a general medical ward where an epidemic of gastro enteritis occurred following a period when the ward was over taxed with cases of respiratory infection Every case of gastro enteritis from this ward was associated with the alpha strain in the stool

After June 1950 testing for the beta type became routine and as you can see this strain became predominant It was my impression that there was at the same time a change in the clinical type of gastro enteritis the cases being much less severe

The incidence of alpha or beta strains on admission is only the beginning of the problem It is important also to find out what happens to these strains as the disease progresses to recovery We have now studied daily rectal swabs on 223 cases during their stay in hospital some in respect of alpha alone others for both alpha and beta strains It must suffice to say that while about two thirds of all clinical exacerbations and relapses are found to be associated with the appearance, or reappearance of alpha or beta strains in the stool it is also found that these strains of *Bact coli* can appear while the patients remain in the ward without clinical deterioration It is possible that a carrier state may exist for some time and this may explain some of these results

Additional serological types of *Bact coli* are now being isolated, and it is suggested that different epidemics are associated with different strains of the organism It is conceivable that the negative observations will diminish as these types become known

The significance of these observations is not quite clear and the

association of the special strains of *Bact coli* with gastro enteritis is not necessarily a causative one but some association there appears to be and further study of the problem would seem to be very desirable

I wish to acknowledge my indebtedness to Professor R W B Ellis and Dr A Joe who have given me the opportunity and the facilities to carry out the work reported *in this lecture and to thank the nursing staffs and the resident doctors who have* looked after the infants in the Royal Hospital for Sick Children and the City Hospital
The chloramphenicol was supplied by the Medical Research Council

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SOME OBSERVATIONS ON CONGENITAL INFANTILE HYPERTROPHIC PYLORIC STENOSIS

By DOUGLAS N NICHOLSON M B F R C P E
Physician Royal Hospital for Sick Children Edinburgh

STUDENTS of medicine during their undergraduate days are fortunate if they have the opportunity of seeing an infant suffering from the manifest symptoms of congenital hypertrophic pyloric stenosis and there are few who have had the good fortune to carry out a detailed clinical examination of such a baby under an experienced demonstrator The clinical knowledge therefore of those medically qualified men and women who go out from our medical schools regarding this relatively common condition is indeed most inadequate

The condition is much more common than is generally believed During the year 1951 out of a total of 3281 children admitted to the medical and surgical wards at the Royal Hospital for Sick Children *in Edinburgh there were 45 cases of congenital pyloric stenosis* That is 13 7 per 1000 admissions or one case in every 73 6 cases was a pyloric

Wallgren reported that of all children born in Goteborg from 1934 to 1940 1 in 250 born developed pyloric stenosis (*i e* 4 per 1000 births) He further found that the incidence was 1 in 770 girls born and 1 in 154 boys born From other observers, such figures as 1 in 213 births (Schæffer and Erbes) to 1 in 400 births (Crammer) have been recorded In 1946 Davison estimated that in Newcastle the incidence was about 3 per 1000 live births in infants born between 1939 and 1942 Figures from different countries will vary depending upon the methods and facilities for examination It would appear that the condition is rare in the Latin races and possibly amongst the Negros

Although congenital hypertrophic pyloric stenosis has been consistently reported as being definitely more common in first born babies and in affecting males I do not feel that these facts should really influence the doctor in his diagnosis as any child may be afflicted regardless of sex or position in the family and there may be two three or even more affected infants in the same family

Read oth November 19,?

Symptoms and Clinical Course

The symptoms and clinical course of pyloric stenosis are usually very characteristic and uniform The first symptom is vomiting which of course is the commonest symptom in any small infant and may be due to many simple factors There are other conditions which may give rise to difficulties in the differential diagnosis and which must be borne in mind (Table I)

TABLE 1

Congenital Infantile Hypertrophic Pyloric Stenosis
Differential Diagnosis

Simple feeding disorder with vomiting
Dyspepsia.
Hyperactive infant with vomiting
Pylorospasm (doubtful as an entity) (functional)
Other causes of high intestinal obstruction
  Congenital bands pressing on duodenum
  Congenital atresia of duodenum
  Congenital diaphragm near pylorus
  Congenital short œsophagus

Mixed adrenal disease
Acquired parenteral disease
  Otitis media.
  Meningitis
  Urinary infections
  Other infections

Enteral infections
  Gastro-enteritis

Œsophageal Thrush

NOTE —Gastric peristaltic waves are occasionally seen in small emaciated infants who do not have congenital hypertrophic pyloric stenosis

The vomiting of congenital pyloric stenosis usually does not begin until ten days to a fortnight after birth although occasionally some vomiting is said to have been present since birth The vomiting may and often does start abruptly but usually begins as a regurgitation of feeds The quantity vomited is at first small but soon it may amount to considerably more than the previous feeding due to gastric retention of the previous feeds and the gastric secretions The vomitus is curdled milk with mucus It is acid in reaction and never contains bile There may be some blood streaks or altered blood present The act of vomiting is forcible and sudden and the ejected contents may be projected several feet and partly through the nose In the early stages it is characteristic that even in spite of the vomiting the baby remains hungry and looks well He is not fretful nor has he the toxic drowsy look of the dyspeptic infant His tongue is clean and he remains very eager for food or drink I have often noted his typical facial expression and it is instructive to watch him feeding Shortly after he has taken a quantity of milk he will quickly show an expression of worry as if

suffering from some slight discomfort He will then suddenly have a forcible vomit which will be associated with a look of disgust and annoyance at the loss of his feed, although sometimes one suggesting relief from slight uneasiness He immediately looks around and if another feed is offered, will once again appear eager for it and the sucking reflex will produce his pouting lips to receive the teat or nipple There would therefore not appear to be any definite symptoms of pain or nausea associated with the early stages of this condition

If the infant continually vomits and little food passes through the pylorus into the intestines, then he will become constipated and quickly lose weight and become dehydrated These are the associated symptoms The constipation will naturally vary according to the amount of milk passing through the pylorus and the stools are usually small and hard but later become scanty dark olive green in colour, soft and slimy—the so called "starvation diarrhœa which is so frequently mis interpreted by the medical attendant

With these suggestive symptoms the diagnosis of pyloric stenosis is made by observing the baby feeding when marked gastric peristalsis is usually seen passing from left to right across the upper abdomen After a feed the stomach often can be seen and felt standing out and tense through the thin abdominal wall

Conclusive evidence of the condition is the palpation of the hard mobile pyloric tumour This is usually situated just beneath the outer edge of the right rectus muscle just below the liver margin It can often be felt even in the absence of visible gastric peristalsis and is usually quite a typical and distinctive clinical manifestation The tumour varies in size from a small pea to that of an olive and it may be very hard or more fleshy to the feel Its characteristic feature is that it is noticed to harden and relax under the examining finger Several careful examinations of the abdomen may be necessary before the tumour is palpated especially where there is a considerable dilatation of the stomach as the pyloric region may then be pushed up under the liver edge or folded behind the dilated gastric organ In these cases I have at times felt the hard tumour come forward and hit my examining finger immediately on the act of the infant vomiting

As there is always a firm tumour in this condition it should be possible to palpate it in every case and it is of interest that at the Royal Hospital for Sick Children during the post war period when the majority of cases have been operated upon the tumour has been clinically demonstrated in 97 3 per cent of cases by more than one observer, and its presence verified at subsequent operation In the literature the palpable pylorus has often not been found I am struck that *in a series of 145 cases treated by operation* at the Royal Hospital for Sick Children in Edinburgh during the period 1922 to 1933 the palpable tumour was recorded only in 24 1 per cent of cases The figures from other authors record a range from about 44 per cent to 100 per cent although most observers claim a positive palpation

in about 90 per cent of cases There are many cases known to us where an operation has been performed in which a pyloric tumour was said to have been felt and where no tumour was found at operation It is thus of importance to have knowledge in this branch of children s work and to have the tumour confirmed by at least one experienced doctor before submitting the infant to operation

I believe that useful information to aid diagnosis can be obtained by passing the stomach tube three or four hours after a feed Not only may a definite gastric retention be proved but also if much heavy milk curd and thick mucus is found a more exact clinical picture is obtained of the physical condition within the stomach For this very simple procedure a soft rubber catheter (6 to 8 English gauge) is used The tip is lubricated with glycerine and slowly passed over the back of the infant s tongue Gentle pressure is kept up and the child continues to swallow The gastric residue can be syphoned off measured and examined The stomach can then be washed out with water or normal saline The careful employment of gastric lavage is in my opinion not only a useful help in diagnosis but also a valuable therapeutic measure in avoiding or alleviating the gastritis which is so commonly associated with gastric retention in these infants The finding of a residue on gastric lavage is not infallible evidence of the delay in the stomach emptying being due to pyloric stenosis as it may be temporarily present in other conditions in infancy which have no organic pathological cause

Some observers particularly in Sweden believe that the diagnosis should always be made by radiology and they insist that not only must gastric delay be shown but that by a special technique a more accurate visualisation of the pyloric canal is made with barium and the repeated demonstration of a much narrowed and elongated channel which is devoid of peristalsis

I have seldom found recourse to radiology necessary in establishing the diagnosis of the manifest case of pyloric stenosis It is possible that mild cases may have been missed as it is known that such cases settle down satisfactorily without treatment owing to their mild symptoms and the natural history of the disease which is self limiting the pyloric difficulty usually being overcome by the fourth or fifth month of life I have seen a child who died at 3½ months of age from an acute encephalo poliomyelitis where a pyloric tumour was found at post mortem and where there was no history or symptoms drawing attention to a pyloric difficulty during life I know of other instances where pyloric tumours have been found post mortem and unsuspected during life

ÆTIOLOGY

Although there is an abundance of literature regarding the ætiology of congenital hypertrophic pyloric stenosis the question is still considered obscure Probably the first case to be reported was in America

suffering from some slight discomfort He will then suddenly have a forcible vomit which will be associated with a look of disgust and annoyance at the loss of his feed although sometimes one suggesting relief from slight uneasiness He *immediately looks around and if* another feed is offered will once again appear eager for it and the sucking reflex will produce his pouting lips to receive the teat or nipple There would therefore not appear to be any definite symptoms of pain or nausea associated with the early stages of this condition

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THE ANATOMICAL AND PATHOLOGICAL PROBLEM

In considering the line of treatment of any condition in medicine we should try to understand the anatomy physiology and pathology of the problem before us What do we know in this respect concerning congenital hypertrophic pyloric stenosis in infants ?

Let us contrast the anatomical appearance of the pylorus of a normal infant with that of one of the same age who has died with congenital hypertrophic pyloric stenosis (Fig 1) In contrast you will note the

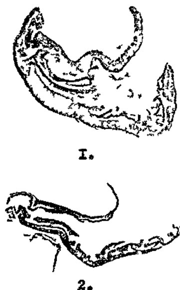


FIG 1 —Longitudinal section of pyloric region from (1) an infant with congenital hypertrophic pyloric stenosis and (2) a normal inf nt of the same age

marked muscular hypertrophy in the region of the pyloric canal This hypertrophy is *confined to the circular muscle coat and consists of* a hard mass which completely encircles the pyloric canal It is fairly well defined at the proximal end although in cases of some duration it gradually blends with the hypertrophying stomach wall proximal to it At the distal end it is well defined and can be seen projecting into the normal duodenum something like a cervix does into the vagina The circular fibres of the pyloric sphincter are not affected (Fig 2) Note position of the pyloric sphincter

On comparing the transverse section of the affected pyloric areas from a nine week old infant with that of a normal infant of the same age John Thomson demonstrated clearly certain important features

by Hezekiah Beardsley, who in 1788 presented a "Case of scirrhus in the pylorus of an infant before the Medical Society of New Haven The case was later republished in the *Archives of Pediatrics* in 1903 In 1887, Hirschsprung described 2 cases of congenital pyloric stenosis and gave an account of the pathological changes He believed that the condition was a primary congenital hyperplasia In 1896 John Thomson recorded 2 cases He also mentioned that the earliest recorded case of the certainly congenital variety of pyloric obstruction which he was able to find was one published by Thomas Williamson of Leith in 1841, where the condition was found at post mortem Thomson believed that a true muscular hypertrophy such as described by Hirsch sprung never occurred as a primary phenomenon, but always as a result of antecedent overaction and postulated some kind of inco ordination between the stomach and the pylorus which had existed for some time previously, probably beginning *in utero* He pointed out that a co ordination between the stomach and pylorus began long before birth when fluids pass through and therefore felt justified in retaining the term ' congenital ' He thought that the essential lesion was not a muscular one but a nervous one— ' a functional disorder of the nerves This view was also held by John Fraser who was a surgeon to the Royal Hospital for Sick Children in Edinburgh for over thirteen years He again pointed out that the hypertrophy did not affect the circular muscle fibres of the true pyloric sphincter He considered it significant that the upset occurred at a situation in which a pure parasympathetic nerve supply merges into an area in which a mixed sympathetic and parasympathetic supply exists He thought that there might be a persistence of motor function without the beneficial influence of inhibition

It seems possible that there may be a congenitally conditioned predisposition to the muscular hypertrophy of the pyloric canal which is linked up with some inco ordination of the nervous mechanism to that region The fact that the condition is so very definitely limited to an age period would suggest that there was some maternal hormonal action either from the placenta or the mother s milk which initiated the muscular hypertrophy No absence of ganglion cells in the submucosa of the affected segment has ever been proved which might have suggested an analogy to Hirschsprung s disease

There are several reports of a definite pyloric tumour being found in premature infants and in still born babies but thi latter finding must be very unusual as Dr Agnes Macgregor in her extensive experience of post mortems on the new born has never seen a case of pyloric stenosis in a still born infant in Edinburgh

A discussion such as this takes us into a wide field of theory and speculation and although the correct answer to the ætiology might give us the solution to our problem regarding the appropriate treatment and management of our cases and hence make my following remarks unnecessary I feel I must leave the intricate puzzle unsolved

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(Fig 3) The increased bulk of hypertrophied circular muscle has produced a tight tube with the peritoneal coat distended to its utmost

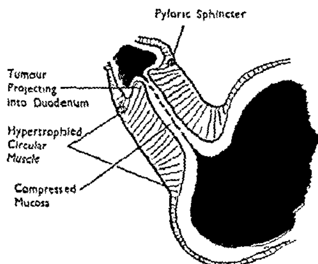


Fig 2 —Diagram—Pathology of pyloric stenosis

limit This outward tension is well shown by the enlarged circumference and circular appearance of the pylorus in contrast with the smaller and softer looking normal pylorus which is obviously not under tension This inability of the serous coat to stretch further

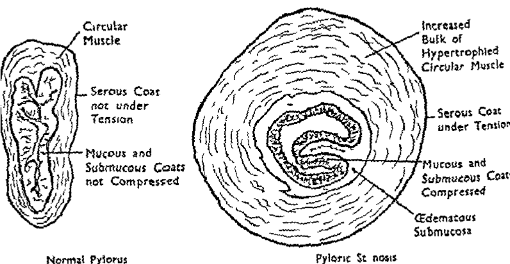


Fig 3 —Transverse section of pylorus near duodenum in infant of nine weeks (after John Thomson

results in the mucous and submucous coats becoming compressed by the hypertrophied circular muscle and thereby probably constituting an important element in the active obstruction caused by the pyloric tumour

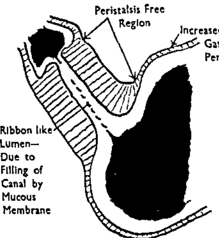
In 1939 Runstrom published a paper on the Rœntgen anatomical appearance of congenital hypertrophic pyloric stenosis during and after the manifest stage of the disease following up his cases over a period of years He studied his cases with a technique to give distinct radio logical details of the mucous membrane relief He demonstrated that during the manifest stage of active symptoms all his cases gave a com pletely uniform radiological picture (Fig 4) For a distance of 2 to 3 cm close to the pyloric opening into the duodenum the pyloric canal was narrowed to a ribbon like lumen Gastric peristalsis was marked but did not pass beyond the oral limit of the constriction The region of the pyloric tumour was devoid of peristalsis The opening time of the stomach was considerably delayed The duodenal cap was normal in shape and size All his cases were treated medically and he observed them from a few up to 13 years of age

When the patients were examined radiologically shortly after the manifest stage he found the pyloric canal was wider and he interpreted this as due to a decrease in the swelling of the mucous membrane a subsidence of the œdema The emptying time of the stomach was normal but still the pyloric 'tumour region was peristalsis free This stage appeared to continue for one to four years

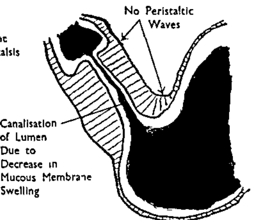
He further demonstrated that with the lapse of time the pyloric canal opened up further and incipient peristalsis appeared in the tumour segment This state of affairs was seen at the earliest age of 2 years and in some cases persisted up to the ages of 8 to 13 years

It would appear from these studies that a child in Runstrom s stage 2 can be symptom free even although the hypertrophied muscular tumour was still well marked and palpable to the examining finger Pædiatricians know that a pyloric tumour can on occasion be felt some time before the visible peristalsis has begun and also that it can be palpated for many weeks after the cessation of manifest symptoms whether or not the infant has been treated by anti spasmodic drugs or only on careful nursing lines We also know that manifest symptoms can disappear only to reappear after a few weeks whether the infant in under medical treatment or not probably due to sudden swelling of the mucous membrane I am convinced that there are many infants who have the condition which never advances beyond this stage 2 and who are never diagnosed as suffering from pyloric stenosis and who have only slight episodes of vomiting with no or little interference with their weight gain and are often explained as simple gastric upsets or are completely ignored

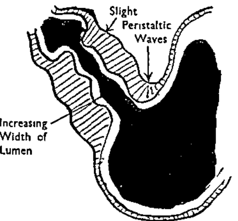
I hope that I have been able to demonstrate that there are at least two reasons for assuming that there is a difficulty to food leaving the infant s stomach These are a rigid peristalsis free tight hyper trophied muscular tumour which is frequently in spasm and also a small lumen blocked by a swollen mucous membrane which can obviously be easily obstructed by milk curds or thick gastric mucus plugs There may be other features of inco ordination of a



Stage of Manifest Symptoms
Age 0 3 or 5 months



No Clinical Symptoms
Age—up to 1-4 Years



No Clinical Symptoms
Age—up to 2 13 Years

Fig 4—Diagram to illustrate the Rœntgen anatomical picture in congenital hypertrophic pyloric stenosis (Adapted from Runstrom)

neuro muscular nature between the stomach and its pyloric end but this has never been proved

We must bear in mind the fact that we are dealing with a human organism which may overcome its pathological difficulties and that there is always the natural tendency to win over adverse conditions Apart from this it is a well accepted fact that the disease is a self limited one in the sense that the pyloric lumen will eventually open up spontaneously and the child recover provided he does not die in the process Medical lines of treatment have been based on the principle of helping the infant to get sufficient food through the pylorus until the natural process of recovery occurs and the management consists of small frequent feeds of a minimal curd forming type possibly with gastric lavage to remove thick mucus plugs which may obstruct the pylorus and the administration of large doses of eumydrin or other anti spasmodic drug hoping to relax the pyloric muscular spasm

TREATMENT

As we do not know the ætiological factors responsible for congenital hypertrophic pyloric stenosis we cannot as yet attack our problem from its prophylactic angle so we do not know the correct line of treatment of the condition and what I wish to try and demonstrate is the best means available to us The aim of any treatment must be to overcome this apparent obstructive difficulty at the pyloric region either by medical or by surgical means

There is a vast literature on the subject of medically and surgically treated series of cases with strong advocates for one or other method of therapy as well as very variable results from both methods of treat ment The opinion of most pædiatricians especially in this country and in America is now in favour of operation

I have already stated that there are many cases of pyloric stenosis which are mild and the slight mechanical difficulty to which it gives rise does not interfere with sufficient food passing into the intestinal tract so that the infant maintains his progress in spite of some vomiting If he is the older child say about 3 months he will quite likely respond to medical management alone although he may at any time show evident acute obstructive symptoms which call for careful review Those infants who show definite manifest symptoms within the first two or three weeks after birth should normally be submitted to operation

The medical lines of treatment are chiefly those of careful nursing and feeding management and not only the administration of increasing doses of eumydrin (atrophine methyl nitrate) This drug is toxic and should not be administered to a dehydrated infant and yet to procure its full action the fluid intake must not be excessive I am not in agreement with the giving of eumydrin as a therapeutic test for pyloric stenosis in a suspected case

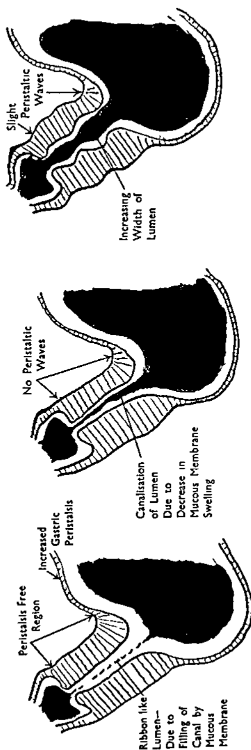


FIG 4 —Diagram to illustrate the Rœntgen anatomical picture in congenital hypertrophic pyloric stenosis (Adapted from Runstrom)

of the condition should be overcome This result appears to be attained and the operation is accepted as most satisfactory and successful as a surgical procedure

The results of healing of the wound over the tumour have been studied by Wollstein who published her report in 1922 She studied pathologically and histologically specimens from a series of cases who died from twenty four hours to two years following operation (Fig 6) The gap between the cut edges of muscle was quickly covered by connective tissue from the serosa and submucosa The muscle cells showed no attempt at proliferation As the muscle coat relaxes the cut edges are slowly drawn together by the fibrous connective tissue of the serosa She states that from nine to thirteen days after operation the wound has healed though the site of operation still shows as a definite depression

It would appear then that the Fredet Rammstedt type of operation cures most of the pathology of congenital hypertrophic pyloric stenosis and that although not the complete answer to the treatment of the condition must be accepted as the best at present available This satisfactory type of surgery gives quick relief of the pyloric obstruction and enables a rapid re establishment of an adequate food intake with only a short period of hospitalisation the infant returning quickly to normal weight and vigour There is no danger of a recurrence in the near or distant future At this stage it is worthy of note that evidence has been produced to show that a hypertrophied pylorus which has not been operated upon may persist into adult life Here I can quote E J Donovan who reported that he had operated upon 2 patients 29 years of age who had had gastro enterostromies performed at the age of 6 weeks for pyloric stenosis In both patients the pyloric tumour was present, looking exactly as it does in infancy Microscopic study of one of these tumours showed that the only abnormal finding was hypertrophy of the circular muscle coat Other such cases have been recorded in the medical literature

The persistence of a pyloric tumour cannot be a common occurrence as I have been unable to trace any case of a child who had suffered from proved pyloric stenosis and who was not treated surgically where a pyloric tumour was discovered at a later abdominal operation or at a *post mortem* With the known frequency of pyloric stenosis in infants surely the surgeons and pathologists would be reporting such findings We do know that congenital hypertrophic pyloric stenosis in the adult is becoming more often recognised although the diagnosis is usually not established until the specimen is removed at operation for a suspected carcinoma or at autopsy It is believed by some that the so called congenital pyloric stenosis of adults is a persistence of the infantile form and the condition has been cured by a Rammstedt s operation in adult life There are a few such cases in the literature which suggest that the patient may have had symptoms referable to a pyloric stenosis in infancy and childhood

If we are to accept surgery as the treatment of choice for the small

Medical treatment calls for a prolonged administration of eumydrin and of careful nursing care and management until the child is at least 5 months of age From studying the anatomical and pathological picture, it is obvious that the administration of eumydrin does not control all the factors which cause the manifest symptoms of the condition

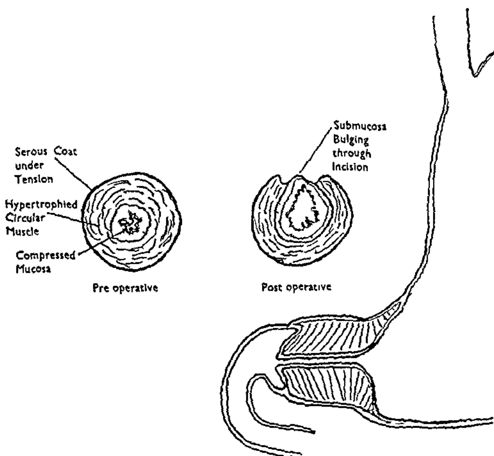


FIG 5 —Fredet Rammstedt operation

It would appear more logical to state that a satisfactory operation would cure all infants with pyloric stenosis The Fredet Rammstedt pyloro myotomy consists of a longitudinal incision from end to end through the hard pyloric tumour This incision must divide all the circular muscle from the pyloric end to the gastric end of the tumour down to but not into the submucosa which then bulges into the wound (Fig 5) I remind you that the size of the pyloric tumour is due entirely to the great increase in the hypertrophied circular muscular coat which is at least two or three times thicker than normal The efficient and complete division of this muscular layer will be followed by a relaxation of this muscle The divided muscle will not now be able to go into spasm and both the mechanical organic and spasmodic features

operation was introduced was about 80 per cent After its introduction there was a reported mortality rate of 18 per cent in 1925 and in 1939 one of 6 5 per cent Reporting from America Ladd *et al* (1946) gave an account of over 1100 cases treated by Rammstedt s operation at the Children s Hospital Boston from 1915 to 1946 with a mortality rate of 3 5 per cent with only five deaths in the last 557 cases and no deaths in the last 225 cases Donovan at the Babies Hospital New York showed an overall mortality of 1 8 per cent in a series of 507 cases treated by operation with only two deaths in 389 cases treated in 1932 to 1947 In 1941 Levi reported a series of 100 consecutive cases treated surgically without a death

In 1934 Wallace and Wevill analysed the records at the Royal Hospital for Sick Children Edinburgh and reported the mortality rate for infants treated by operation over the twelve year period 1922 to 1933 to be 24 8 per cent (Table II)

TABLE II

Cases of Congenital Pyloric Stenosis admitted Royal Hospital for Sick Children Edinburgh

Year under Review	1922 to 1933	1946 to 1951	1951	1952 Jan Oct
Number of cases admitted	210	358	45	37
Number treated by operation	145	33	4	37
Number treated medically	65	26	3	Nil
Number of deaths operation cases	36	5	Nil	Nil
Mortality rate operation cases	24 8 per cent	7 5 per cent	Nil	Nil

I have found that during the six year period 1946 to 1951 the mortality rate for surgically treated cases had fallen to 7 5 per cent Of the 45 cases admitted during the year 1951 41 were treated by operation with no deaths and during the first ten months of the present year 37 cases have been admitted all of which have been operated upon with no deaths

There are many reasons why our results of operative treatment have been showing this definite improvement The surgical technique has remained more or less the same throughout the periods under review and it is seldom that the infant dies as the result of an unsatisfactory operation

The general practitioner is more aware of the possibility of the disgnosis and cases are referred to hospital for advice earlier than they were some twenty years ago with the result that the infants are consequently in much better condition when first seen by the pædiatrician In the 1922 33 series of admissions the average duration of symptoms before admission to hospital was 3 8 weeks whilst in the 1946 51 series it was 2 5 weeks The pædiatricians do not persist with long periods of medical treatment until it has failed and leaving surgery as the only hope We have learned a great deal about infant physiology

infant with manifest symptoms of pyloric stenosis we should review the records of the past and present in this particular field of study I do not intend to critically compare the results obtained by medical

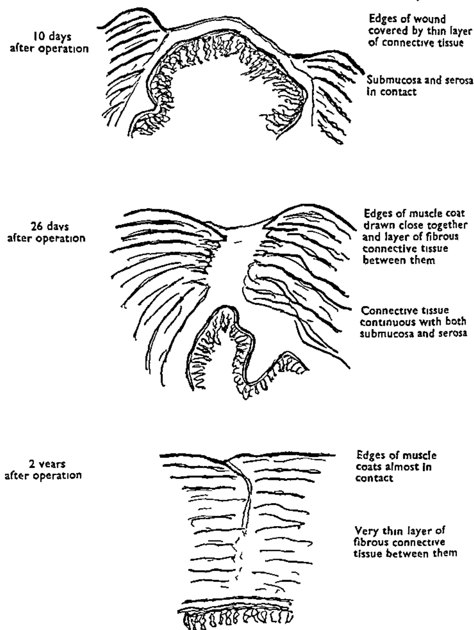


FIG 6—Healing of wound after Fredet Rammstedt operation (After Wollstein)

lines of treatment with those from surgery but in passing would like to comment on the very definite trend towards surgery in this country as well as in America over the past ten to twenty five years

The mortality rate for infants suffering from pyloric stenosis at the Hospital for Sick Children Great Ormond Street before Rammstedt s

post operative condition of many of the infants could have permitted their discharge at an earlier date

It is of some interest to compare a series of 71 cases from the years 1951 and 1952 where there was no deaths with a series of 109 cases from the period 1946 to 1951 where the mortality rate was over 7 per cent (Table III) It is seen that the serious operative complications appear to be associated with the anæsthetic management in the earlier

TABLE III

Post Operative Complications

	1946–1951 (109 Cases) Mortality Rate 7·6 per cent		1951 and 1952 (71 Cases) Mortality Rate Nil	
	Number of Cases.	Death	Number of Cases	Death
OPERATIVE COMPLICATIONS—				
Post operative pulmonary collapse and aspiration pneumonia	6	6	0	0
Post operative apnæa	2	0	0	0
Incomplete division of pyloric tumour	1	1	1	0
Hæmorrhage from operation wound	2	0	1	0
Post operative hæmatemesis	3	0	3	0
INFECTIVE COMPLICATIONS—				
Vomiting and/or diarrhœa due to infection *e g* gastro enteritis	6	4	6	0
Upper respiratory tract infections	4	0	3	0
Otitis media	6	0	-	0
Wound sepsis (superficial)	2	0	3	0
MECHANICAL COMPLICATIONS—				
Frequent stools without evidence of infection	12	0	8	0
Frequent vomiting (over 4 days) without evidence of infection	21	0	1	0

group and that now this has been overcome In the infective group bowel infection was the most frequent complication

I have grouped the passage of frequent stools and the occurrence of vomiting for more than four post operative days as mechanical complications as in these cases no evidence of infection could be determined and the symptoms cleared up without any antibiotic or chemotherapeutic remedy The infant who has had a pyloric difficulty for some days may naturally have a tendency to vomit after relief of the obstruction from failure of the mechanism of the stomach to co ordinate and a bowel which has not been receiving its normal amount of solid food over a period will react with an increased peristal is to a sudden flow through the now open pylorus The recognition and correct management of these symptoms is of great clinical importance and I believe bears out the necessity for the very slow introduction of

and that it is the restoration of fluids and electrolyte balance that is so urgent in these babies It is the effects of starvation and dehydration the loss of chlorides and other biochemical changes produced by persistent vomiting which need to be completely remedied before the infant is subjected to operation The operation itself is not an emergency and it is very unwise to hasten one before you are convinced that the *infant is unlikely to be further improved by your efforts* The time necessary to correct the effects of dehydration and the restoration of proper electrolyte balance is not only well spent but is essential to a good surgical result The average number of pre operative days in hospital for the recent series was four days

Infants are still often admitted to hospital in a fairly severely dehydrated condition and this calls for the closest co operation between the physician surgeon and nursing staff and I strongly advise such an infant's transference to a pædiatric unit where all the understood measures of infant management can be carried out At the Royal *Hospital for Sick Children these infants are now normally admitted* under the physician s care for pre operative and post operative care in co operation with the surgeon

The surgeons have carefully assessed their operation procedure and this includes the experienced anæsthetist the maintenance of warmth during operation etc The operation itself lasts only a few minutes under a light inhalation anæsthesia along with a local infiltration and the baby is returned to the medical ward fully awake and able to cry so that he can expand his lungs actively and is in possession of his active reflexes

In the post operative care there are many facts of importance It must be appreciated that an operation itself is followed by definite metabolic changes and water and electrolyte upset which are a normal response to injury and these must be anticipated The gastric emptying time is probably nearly always considerably delayed following operation and care must be taken in offering fluids orally in the immediate post operative period Following the slow introduction of small quantities *of glucose saline in increasing amounts it is usually found that a* small feed of breast milk or some easily digestible formula can be offered within eighteen or twenty hours after operation If there is no vomiting or bowel frequency the feeds can usually be rapidly increased in amount and strength I believe that it is much better to have the infant hungry with its electrolytes and fluids controlled by oral or parenteral salines over the first day or two after operation than upset by too early *administration of a milk feed If he is well when* feeding is later started he will soon make up his weight and progress He should be a normal baby within a few days following his operation and fit for discharge from hospital On the average the infants of the series were discharged on their ninth post operative day In assessing this figure however must be taken into account such social factors as unsuitable home conditions and distance from hospital The general

urgent feature For this a clear understanding of infant physiology is necessary Infants become dehydrated much more rapidly than do adults and the conditions produced by this water loss along with the disturbed electrolyte balance may carry a high fatality This upset medical condition is the emergency and must be understood The persistent vomiting leads to a loss of water but also to chlorides in excess of base thus producing both dehydration and alkalosis for which it is difficult for the infant s body to compensate The sudden loss of weight associated with this vomiting is due to depletion of electrolytes which must be quickly restored by the administration of solutions of sodium chloride along with glucose to overcome the ketosis and replenish the liver glycogen Sufficient water and electrolytes must be given to restore and maintain the normal fluid make up of the body without endangering the infant s life by flooding its circulation with intravenous fluid Intravenous fluids must be given very slowly as it is easy to precipitate circulatory failure with pulmonary oedema However in cases of very severe water and electrolyte upset this method is necessary and urgent Most cases require only subcutaneous isotonic or half isotonic salines with glucose and it is now more usual to aid their absorption by the use of hyaluronidase

The successful management of the infants with this condition is co operation of trained pædiatric personnel in which the physicians surgeons anæsthetists and nursing taff all play their vital parts The condition which not long ago was a most serious and worrying one has now lost most of its terrors

I wish to express my thanks to Dr Agnes Macgregor for permission to use the slide of the normal and pathological pyloric segments and for her valued help and advice in a discussion of the pathology To my Pædiatric Registrar Dr Ian C Lewis I am grateful for his help in reviewing the hospital case records

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fluids and food orally in the early post operative days The average day for the passage of the first post operative stool in my series was 2 5 days Frequent post operative vomiting or loose frequent stools will tend to upset the fluid and electrolyte balance and render the infant more liable to infection Of the series, 54 9 per cent of infants had no post operative vomiting 5 9 per cent had regurgitations only 18 6 per cent had vomiting for one to four post operative days and 20 6 per cent had frequent vomiting lasting five days or more

I have many charts illustrating the successful management of cases of congenital pyloric stenosis treated by operation These charts clearly show that with careful pre operative care satisfactory operative and post operative procedures these babies were again normal healthy and happy within a few days of their hospital admission and could almost be imagined to say in the words from *Hamlet* For this relief much thanks '

Conclusion

Congenital hypertrophic pyloric stenosis in infants is commoner than is usually believed and an awaredness of the condition must be borne in mind so that an early diagnosis can be made while the infant is still in a good physiological state

Many cases may not require any further care than the offering of small frequent digestible feeds, with or without the administration of eumydrin The giving of eumydrin *per se* without the essential feeding care is bad medicine and to be deprecated It should certainly never be permitted in the small infant with acute manifest symptoms and signs of dehydration Medical lines of treatment may be preferred for infants of eight to twelve weeks of age especially where symptoms are not severe and the infant is maintaining his weight Medical treatment of the small infant will call for many weeks of continual supervision until he is at least five months old

Surgical treatment is recommended for infants who show manifest symptoms during the first few weeks of life More certain and quicker results are obtained by a relatively simple surgical procedure and the parents can be assured not only that their baby may be operated upon successfully and that he will be retaining all his feeds and gaining weight within ten days after operation but also that he will not have any trouble from his stomach in later life as a result of his pyloric stenosis in infancy It is now unusual for a pyloric baby to have anything but a most uncomplicated convalescence after operation

To procure this high attainment from surgery however it is most desirable that the infant is under the care of those physicians surgeons and nursing staff who are fully trained in the management of such babies and they should be referred to pædiatric centres wherever possible

It is essential to appreciate that the operation is not an emergency and that it is the preparation of the infant for operation which is the

stand unchallenged to dav For example he recognised not only that a diabetic woman might become pregnant but that a pregnant woman might become diabetic and that her diabetes might disappear in the puerperium only to return at a later date He found that the prognosis was poor both for the mother who ran a grave risk of death in diabetic coma and for the child whose chance of survival was less than 50 per cent

In 1909 at the end of a period which had yielded much information about the natural history of diabetic pregnancy in the days before insulin was available Whitridge Williams reviewed the position He confirmed the high maternal mortality quoting from the literature estimates which varied between 25 and 55 per cent The fœtal mortality was no less and amounted to 47 per cent in the series of 66 cases which he collected from the literature Overgrowth of the child resulting in difficult delivery was recognised to be the cause of some of the fœtal deaths but it was also apparent that the fœtus tended to die in the uterus during the last month of pregnancy and to be delivered in a macerated condition Williams stressed the danger of ketosis to the mother and recommended that the pregnancy should be terminated if such a complication arose He also recognised that hydramnios was common and that the amniotic fluid often contained much sugar

There were two reasons for the rarity of diabetic pregnancies in the pre insulin era The first was that relatively few women of child bearing age were diabetic because young diabetics seldom survived for more than three years after the onset of the disease and the second that the young diabetic woman was usually infertile and often had amenorrhœa

The literature of those days is difficult to follow because there was much confusion between diabetes and other causes of glycosuria and it seems probable that a proportion of the cases reported as diabetic were in fact examples of renal glycosuria which we now recognise to be particularly common in pregnancy

Little further advance was made before the introduction of insulin but it was noticed that in a few cases the maternal diabetes became less severe towards the end of the pregnancy and an interesting controversy arose as to whether or not the fœtal insulin could pass the placental barrier and be responsible for this amelioration This question has a direct bearing on subsequent attempts to reduce neonatal mortality and will be referred to later

INSULIN

The introduction of insulin raised new hopes for the pregnant diabetic but while it has solved some of her problems others remain little affected by this major advance in treatment In the insulin era the pregnant diabetic has ceased to be a medical curiosity and any large maternity hospital now makes special provision for the care of these patients of whom we see approximately 20 in the Simpson

DIABETES IN PREGNANCY

By CHARLES ROLLAND B A, M D M R C P E
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INTRODUCTION

My subject to day represents a common ground on which the physician and the obstetrician meet and to which they summon the biochemist the pædiatrician the pathologist and others for guidance and assistance in their attempts to conduct the diabetic pregnancy to a safe and happy conclusion Diabetes in pregnancy has three particular fascinations for the physician In the first place he has often known his patient for some years and looks forward to seeing her bring up her family Secondly success in the form of a living child is by no means assured and there are many intriguing problems which remain to be solved And last but by no means the least is the privilege of a close association with his colleagues in the other specialities, without whose help his own efforts would be of little avail Team work is essential and I would like at this early stage to acknowledge my gratitude to all those who have helped in this task and particularly to Dr Douglas Matthew with whom I have worked for the past five years

HISTORICAL

Our Victorian grandmothers used to describe pregnancy as an interesting condition but in their day the pregnant diabetic must have been peculiarly interesting because of her extreme rarity Bennewitz of Berlin was apparently the first to record the fact that a diabetic woman could bear a child and his paper of 1826 must have aroused some interest in Edinburgh for a summary of it was published in the *Edinburgh Medical Journal* of 1828 His patient set the fashion for many of her followers by having a premature labour and bearing a stillborn baby weighing no less than 12 lbs whose size so impressed Bennewitz that he was tempted to attribute its paternity to Hercules

In 1882 Matthews Duncan was able to collect only twenty two instances of diabetic pregnancy from his own experience and a study of the literature He made a series of conclusions many of which

Read 14th May 1953

Before discussing the fundamental causes of the fœtal mortality we must consider the various ways in which fœtal deaths occur Table I shows an analysis of the fœtal loss in this series of cases

Abortions—Most authors agree that the incidence of spontaneous abortion is not increased in the presence of maternal diabetes but it is notoriously difficult to obtain accurate figures on this subject Nevertheless it seems fair to conclude that well controlled diabetes is not a factor which contributes to abortion Diabetes itself is no longer considered to be an indication for therapeutic abortion but on occasion the vascular complications of long standing diabetes may warrant such an interference There were three spontaneous and two therapeutic abortions in our series and of the latter, one was in an unstable half witted diabetic dwarf with severe retinitis and the other was in a woman

TABLE I

Diabetic Women—64 Total Pregnancies—77
(7 had 2 pregnancies 3 had 3 pregnancies)
Live Births—55

Abortions	Spontaneous	3	
	Therapeutic	2	
	Ectopic Gestation	1	
Intra uterine Death		9	Total Mortality Viable Infants—16
Stillbirth			
Neonatal Death		5	

Total Fœtal Loss—[illegible]2

Overall Fœtal Loss Rate 28 6 per cent
Fœtal Loss Rate Viable Infants only 2[illegible] 5 per cent
Maternal Mortality Nil

who was blind as the result of retinitis and who had a diabetic nephropathy Both these patients had had diabetes for more than fifteen years

Intra uterine Deaths—Intra uterine death of the fœtus between the thirty fifth week and term has long been recognised as common in the pregnant diabetic and there were 9 such cases in our series The cause of these intra uterine deaths is unknown and they remain one of the most perplexing problems in connection with this work Some occur in patients who suffer from pre eclampsia and in such cases the two events may well bear more than a temporal relationship but intra uterine deaths are often seen in the absence of toxæmia and it is evident that this disease is not entirely responsible for these catastrophes

Stillbirth—We have already seen that the fœtus of the diabetic mother tends to grow to a larger size than that of the non diabetic and it is not uncommon to find that an infant weighing 10 lbs is born at or before term In the past such an event was attended by a high incidence of stillbirth as a result of injury to the fœtus during a difficult labour Naturally in these circumstances maternal injury and exhaustion were also common These dangers are now well recognised and are usually avoided by premature termination of the pregnancy either by induction of labour or by Cæsarean section There were two

Memorial Maternity Pavilion each year This increased incidence is due to two changes The expectation of life in the young diabetic woman has increased to about five times that of the pre insulin era and this together with the greater incidence of the disease, means that the number of diabetic women in the child bearing years is much larger than it was or to put it another way, the population at risk has increased Moreover the diabetic woman when well treated with insulin, is almost as fertile as her non diabetic sister and though we still encounter amenorrhœa in the presence of uncontrolled diabetes it is no more common in the well treated patient than in the non diabetic

One of the most notable results of the use of insulin is the reduction in the maternal mortality rate which has fallen to below 2 per cent in any well conducted series of cases Here in Edinburgh during the last four years, we have had a series of 77 pregnancies in 64 diabetic women without a single maternal death This salutary change is a reflection of the fact that severe ketosis can be prevented by an intelligent use of insulin and corrected rapidly if it should chance to arise On the other hand the maternal morbidity remains greater than it is in non diabetic pregnancy Hydramnios is a common complication and while it is seldom severe enough to cause great discomfort it is a sign that all is not well Pre eclampsia is a common feature of diabetic pregnancies and though views on its incidence vary considerably there are few authors who do not emphasise its importance

Fœtal Mortality

Despite this great improvement in the outlook for the mother the use of insulin was not followed by an immediate fall in the fœtal mortality which remained as high as 50 per cent until recent years when it has fallen to between 15 and 25 per cent in many of the clinics where particular interest is taken in diabetic pregnancies It is sometimes difficult to compare figures for the fœtal loss rate, because the meaning of this term is not always clearly stated I use the phrase ' overall fœtal loss rate in reference to all pregnancies which did not result in the birth of a child who survived for at least fourteen days and I include all the women delivered irrespective of the duration or adequacy of their antenatal care In Edinburgh we have had an overall fœtal loss rate of 28 6 per cent in the past 77 cases a figure which compares favourably with one of 51 4 per cent in the previous 70 cases in the Simpson Memorial Maternity Pavilion (Gilbert and Dunlop 1949) If we exclude all the cases which terminated in delivery before the twenty eighth week of pregnancy and this is what many authors do the figure of 28 6 per cent is reduced to one of 22 5 per cent

The raised fœtal mortality rate remains the supreme problem in diabetic pregnancy and much of the attention of those who work in this field has been devoted to finding the cause of fœtal deaths and to devising means whereby they can be prevented

pregnancy approaches term but in my experience this is a rare event One might also expect that the removal of the source of extra insulin at the time of delivery would be followed by an immediate rise in the maternal insulin requirements whereas the reverse is usually seen as is shown in Fig 1 The profound fall on the day of delivery is due to the fact that the muscular exertion of labour is accompanied by an increase in the rate of glucose utilisation which leads to hypoglycæmia if the dose of insulin is not reduced and in the cases delivered by Cæsarean section the carbohydrate intake is necessarily very limited on the day of the operation After the birth there is a gradual rise in insulin requirements for about five days after which the dose usually remains steady at a considerably lower level than that given immediately

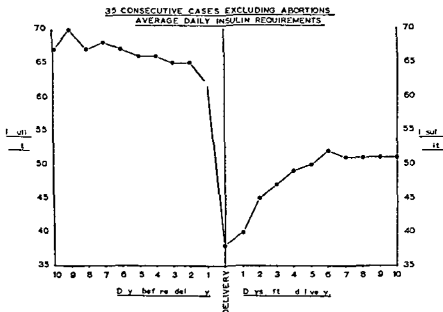


FIG 1

before delivery When the patient returns home a further fall in insulin requirements takes place and the dose stabilises at a level which is very similar to that of the same individual before she became pregnant Hypoglycæmia is in consequence a common complication in the early puerperium unless these changes in insulin requirements are anticipated

THE PRE DIABETIC STATE

The next step must be to consider the attempts that have been made to explain the high incidence of intra uterine death and overgrowth of the fœtus In the past several authors have concluded that the fœtal loss rate was particularly high in cases where the maternal diabetes was poorly controlled (Lawrence and Oakley 1942) or where the insulin requirements were high but all such hypotheses have been rudely upset by the discovery by Allen in 1939 that women who were

stillbirths in our series one as the result of a difficult delivery and the other in a premature labour at the thirtieth week In neither case was the baby of exceptional size

Neonatal Deaths—There were 5 neonatal deaths in our series and this is in line with the general experience that the new born child of a diabetic woman is a delicate creature whose early life is precarious in the extreme There are two main views as to the cause of these neonatal deaths The first and probably the most important, is that the majority of the infants are delivered at a premature stage of their development a fact which may escape the notice of those who are accustomed to estimate maturity in terms of the body weight of the child, for these babies may weigh more than 7 lbs at the thirty sixth week In addition to their prematurity they suffer from other defects which may contribute to their poor viability Many of them are œdematous and have enlargement of the heart liver and other viscera together with other pathological features which have encouraged Miller and Wilson (1943) to liken them to the infant which suffers from erythroblastosis fœtalis Congenital defects are often listed among the causes of fœtal death, but their importance has been over emphasised Only one death in our series resulted from a congenital defect, and that was an anencephalic baby Symptoms of respiratory distress are common in these infants They often breathe well for a short time after birth and then become subject to irregular respiratory movement attacks of cyanosis and even periods of apnœa Neonatal death is particularly common in babies who show these respiratory symptoms but skilled nursing with special attention to the drainage of the respiratory tract and maintenance of an adequate supply of oxygen leads to a considerable reduction in the neonatal mortality

The other important view is derived from the concept which I have already mentioned that the fœtal pancreas may compensate for the lack of maternal insulin during the later weeks of pregnancy and that in consequence the infant may be born with an over active pancreas and may suffer from hypoglycæmia during its early life This hypothesis is supported by two observations Many workers have demonstrated hypertrophy of the islets of Langerhans in a proportion of the offspring of diabetic mothers and it has been shown that the child s blood sugar falls after birth at a greater rate and to a lower level than that of the new born of a non diabetic woman In many hospitals glucose is administered at birth and for the next two days in an attempt to combat hypoglycæmia but it remains uncertain whether hypoglycæmia is a grave danger to these infants Our own data have not been analysed in full but in common with others we have a strong impression that if hypoglycæmia is of any importance it is only a contributory and not a primary factor in the cause of neonatal death

It is reasonable to assume that if fœtal insulin plays any considerable part in the control of maternal carbohydrate metabolism it would be common to find the mother s daily insulin requirements falling as the

of such a baby may be the first sign that a woman is destined to develop diabetes later in her life A hypothesis has been advanced which explains the overgrowth of the fœtus the subsequent development of maternal diabetes and the high fœtal loss rate as separate manifestations of a single abnormality—the over production of the growth hormone by the anterior pituitary of the mother We know that growth hormone can in certain circumstances cause excessive growth whereas in others it can cause diabetes and that the two events are sometimes seen in one individual for the diabetic child has often undergone a period of abnormally rapid growth immediately before the onset of his disease Nevertheless there is an obvious objection to the hypothesis in the fact that neither pre diabetic nor diabetic women commonly show any of the classical features of acromegaly and final judgment must await the development and application of an accurate method for the assay of growth hormone in the body fluids

HORMONAL IMBALANCE

Another line of attack on the problem, again invoking the endocrine system began when Smith and Smith (1933) found that a number of women suffering from pre eclampsia had abnormally high levels of chorionic gonadotrophin in both the blood and the urine This finding was followed by the observations that the urinary excretion of œstrogens and pregnanediol was abnormally low in these toxæmic women (Smith and Smith 1934 1938) In a long series of papers the Smiths developed their view that this hormonal imbalance as they call it is of importance in the ætiology of pre eclampsia and the increased fœtal loss which accompanies this condition Their patients included a number of diabetics who were studied because of their susceptibility to pre eclampsia As a result of their work the Smiths evolved a theory which attempts to explain the mechanism of the production of toxæmia but which is complex and need not be considered in detail (Smith and Smith 1948) Its main principle states that the features of the disease result from the release of a toxin from the placenta when its integrity is impaired by an interference with its blood supply This interference may be due to a variety of causes and it has been suggested by White (1952) that degeneration of the pelvic vessels in long standing diabetes may be one of them She has actually demonstrated calcification of these vessels in a number of her pregnant diabetics so far we have found such calcification in only one case and that was not attended by fœtal death Whatever the initial cause of the toxæmia may be the Smiths consider that a deficient production of œstrogens is an intermediate factor From the more practical point of view the Smiths believe that the development of the hormonal imbalance is a warning of the imminence of toxæmia and of danger to the infant They state that the imbalance can be corrected by the administration of diethylstilboestrol and that the dangers to both mother and child can be averted by this means

destined to become diabetic in later years that is pre diabetic women, had an obstetric history characterised by a high fœtal mortality and the birth of large babies Allen s conclusions have been supported by many and challenged by very few and it is now widely accepted that a metabolic abnormality may exist for as long as twenty years before the onset of clinical diabetes and that this pre diabetic state is characterised by a high rate of fœtal loss and the frequent birth of babies weighing more than 10 lbs In the five years immediately preceding the onset of diabetes the obstetric history is indistinguishable in these respects from that after the disease has developed Table II shows the obstetric history of the 64 diabetic women in our series

TABLE II

64 Diabetic Women Obstetric History Before and After Onset of Diabetes

	Y ars.	P g n s.	Abo t ns	Stillb rth I t Ute D ath	Neo t l D th	Fœt l L s.	L B th	Fœ al Los R te P C t.	O lb	L der 1 lb.
Pre Diabetic State	16+	12	0	1	1	2	10	16 7	6	5
	11 15	17	0	1	0	1	16	5 8	4	12
	6 10	16	0	3	0	3	13	18 ,		7
	0 5	33	6	5	2	13	20	39 9	5	!
	Total	78	6	10	3	19	59	4 4		45
Diabetes	0 5	58	2	10	1	13	45	2 4	7	46
	6 10	3	4	6	4	14	9	60 9	0	19
	11 15	7	1	0	1		5	28 6	0	6
	16+	8	-	0	0	2	6	25 0	0	6
	Total	96	9	16	6	31	65	32 3	7	77

including their pre diabetic and diabetic pregnancies It shows the high pre diabetic fœtal loss 24 4 per cent in 78 pregnancies, and that more than half of these deaths fell in the group of stillbirths and intra uterine death It also shows the high incidence of babies weighing more than 10 lbs at birth 22 out of 78 pre diabetic pregnancies com pared with only 7 out of 96 diabetic pregnancies This latter figure is artificially reduced by the early delivery of many of the diabetic women The numbers are not large but the figures correspond closely with those of larger series

The recognition of this pre diabetic state is of great interest and has led to much speculation It is obvious that a factor which is independent of maternal hyperglycæmia and which operates for as long as twenty years before the onset of diabetes produces the obstetrical abnormalities which were once thought to be characteristic of diabetic pregnancy This has been emphasised by Miller (1945) who reported that some of the infants of pre diabetic mothers have hypertrophy of the islets of Langerhans and other pathological features which he has found in the new born of diabetic women He goes so far as to say that the birth

of chorionic gonadotrophin in both the serum and the urine but he has found that stilboestrol therapy, even in high doses effects only a transient reduction in these levels (Loraine 1949) We have been unable to correlate the high levels of chorionic gonadotrophin with the severity of the diabetes the incidence of toxæmia the birth weight of the baby or the fœtal loss rate Tables III IV and V and Fig 2 show a comparison between the pregnancies with fœtal loss and those with fœtal survival in respect of the high levels of chorionic gonadotrophin In drawing up these Tables I have excluded all those cases which terminated in abortion and all the assays which were done in the first one hundred days of pregnancy After the one hundredth day a figure in excess of 11 000 international units of C G per litre of serum or per twenty four hours output of urine may be considered to be abnormally high and the results have been divided into those above

TABLE III

Serum Chorionic Gonadotrophin After 100th Day

Outcome of Pregnancy	Cases.	Estimation	Average Estimation Per Case.	Per cent. Estimation > ,000 I U Per Litre.	Per cent. Estimations < ,000 I.U Per Litre.
Fœtal loss	9	34	3 8	23 5 per cent	6 5 per cent.
Fœtal survival	28	175	6 25	21 7 per cent	78 3 per cent.

TABLE IV

Urine Chorionic Gonadotrophin After 100th Day

Outcome of Pregnancy	Cases.	Estimations.	Average Estimation Per Case.	Percentage Estimation > ,000 I U Per 4 Hrs.	Percentage Estimation < ,000 I U Per 4 Hrs.
Fœtal loss	14	115	8 2	44 3	55 7
Fœtal survival	34	325	9 5	28 6	71 4

TABLE V

Urine Chorionic Gonadotrophin After 100th Day
(Case 24 Omitted)

Outcome of Pregnancy	Cases.	Estimations.	Average Estimation Per Case.	Percentage Estimation > ,000 I U Per 4 Hrs.	Percentage Estimation < ,000 I U Per 4 Hrs.
Fœtal loss	13	82	6 3	23 2	76 8
Fœtal survival	34	325	9 5	28 6	71 4

Hormone Therapy

The work of the Smiths has been supplemented by that of Priscilla White who works in Joslin's clinic in Boston and has an unrivalled experience of pregnancy in the diabetic She believes that the hormonal imbalance is a factor of the first importance in the bad obstetric history of these women and claims that it can be corrected by the administration of stilboestrol and progesterone both of which she gives in large doses by daily intramuscular injection Furthermore, she claims that this treatment improves the prognosis for the fœtus and reduces the incidence of maternal toxæmia In a series of 525 diabetic pregnancies, excluding abortions she has had a fœtal mortality of 16 per cent She divides her series of cases into three groups the first of which numbering 47 had normal hormone levels were not treated with stilboestrol and progesterone and had a fœtal mortality of 4 per cent The second group consists of 98 cases which, though they had hormonal imbalance were not treated and had a fœtal loss rate of 44 per cent The third group comprises 380 cases who likewise had hormonal imbalance but were treated with stilboestrol and progesterone and had a fœtal loss rate of only 10 per cent (White 1952) At first sight these figures seem to afford strong support for the value of the treatment with stilboestrol and progesterone but White s conclusions have been the object of much criticism Pedowitz and Shlevin (1952) claim that results of the same order as White s can be obtained without recourse to the arduous and expensive hormone therapy It has been emphasised that White s conclusions depend upon the use of her second group of patients those with hormonal imbalance and no therapy as a control for her third group, those with hormonal imbalance who were treated and several authors criticise this point on the grounds that the control is inadequate (Hurwitz 1941) White s results are difficult to interpret because her patients are delivered well before term and 65 per cent of the 525 cases have had a Cæsarean section a procedure which has given good results in other hands despite the lack of hormone therapy

Hormone Assays

In a number of our cases the chorionic gonadotrophin has been estimated in both the urine and the serum by Dr J A Loraine and the urinary pregnanediol has been estimated by Mrs E Michie both of whom work in the laboratories of the Clinical Endocrine Research Unit and to whom I am very much indebted for the results of their assays They have used methods which differ from those employed by Priscilla White which makes it difficult to compare the results obtained The gonadotrophin assays were done by the method of Loraine (1950) and the pregnanediol was estimated by the short method of Somerville Marrian and Kellar (1948) Dr Loraine s figures confirm that a proportion of pregnant diabetics have an abnormally high level

there is no real difference between the patterns of the two groups Some of the figures in fœtal loss cases in the later stages of pregnancy were obtained after the fœtus had died in the uterus and are consequently low This accounts for most of the crosses to be seen at the lower right corner of the graph It is also of interest that the overall picture shown by the scatter graph differs very little from one prepared by Mrs Michie from assays made by the same method in a series of normal pregnancies (Michie 1953) It seems that serial pregnanediol estimations by this method are of no more prognostic value as to the fate of the fœtus than the assays of chorionic gonadotrophin

Hormone Therapy

Our experience of hormone therapy has been limited but if we exclude abortions there were 54 cases who had no hormone therapy

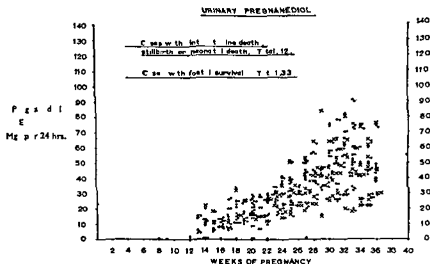


Fig 3

(other than insulin) with a fœtal mortality rate of 22 2 per cent and there were 17 cases who were treated with stilboestrol and progesterone or ethisterone in various doses mostly of the same order as those used by White and in this group the fœtal mortality rate was 23 5 per cent These numbers are small by comparison with White s but so far as they go they do not support her views on the value of hormone therapy It is true that there has not yet been a report of a large scale repetition of White s work using adequate controls but the impression which one forms from a number of small series which have been published and from hearing of unpublished work is that others are failing to show that hormone therapy reduces the fœtal loss rate As is so often the case the enthusiastic reception of a new approach to a problem is being followed by a gradual abandonment of the hopes which were raised

and below this figure Table III shows the results of the serum assays Although the figures in the fœtal loss group are small, *there is no* significant difference between the incidence of high readings in the two groups Fig 2 shows these readings expressed in the form of a scatter graph with the fœtal survival group represented by dots and the fœtal loss group represented by crosses It will be seen that there is no clear difference in the pattern formed by the two groups Table IV shows the urine assays expressed in a table and here it appears that the incidence of high readings was greater in the fœtal loss group 44 3 per cent compared with 28 6 per cent The importance of these figures may well be doubted if we see what happens when a single case is

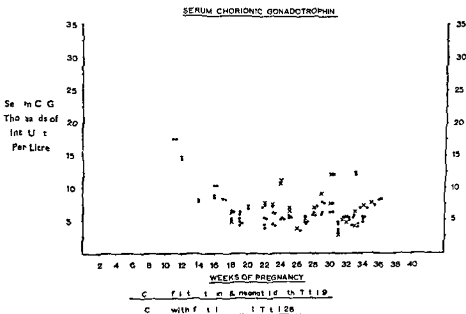


Fig 2

omitted from the fœtal loss group as is shown in Table V where there is a preponderance of high readings in the fœtal survival group The case omitted was one in which an unusually large number of assays were done and whose readings were almost all high The baby in this case made good progress *for the first week of its life and then died of* pneumonia after the aspiration of a feed an unfortunate event which could hardly be attributed to the maternal diabetes and but for which the case might well have been included in the fœtal survival group These facts show how difficult it is to interpret results of this sort but we can only conclude that in our cases and with our methods the finding of high levels of chorionic gonadotrophin in an individual patient has been of no prognostic value *with regard to the fate of the* fœtus

Fig 3 shows the pregnanediol estimations expressed as a scatter graph with the same distinction between the assays in cases with fœtal loss and those in cases with fœtal survival Here again

of 71 deliveries were conducted between the thirty fifth and thirty eighth weeks Possibly the 4 intra uterine deaths which occurred after the thirty sixth week could have been prevented by earlier delivery but in one of these cases the patient was first seen after the baby had died and in another the patient had left hospital against advice and returned with a dead child

It is impossible to be dogmatic about the manner in which these early deliveries should be conducted The choice lies between Cæsarean section and induction of labour and our general rule has been to advise Cæsarean section in all cases unless there is a history of previous un complicated vaginal delivery Cæsarean section is conducted under spinal anæsthesia and is without doubt the most certain means of obtaining a live child in these early deliveries since it protects the infant from mechanical stresses of labour and the chemical stresses

TABLE VII

Mode of Delivery Related to Result of Pregnancy Excluding Abortions

Mode of Delivery	Total Cases.	Intra Uterine Death.	Stillbirth.	Neonatal Death.	Live Birth	Total Fœtal Loss.
Cæsarean section	43	1	0	3	39	4
Vaginal delivery	28	8	-	2	16	1

of analgesic drugs which might be used during labour Some workers have criticised the practice of early delivery on the grounds that it simply transfers the fœtal deaths from the period of late pregnancy to the early puerperium This may be true where the neonatal care is imperfect but it has not been our experience as can be seen in Table VII which compares the fates of the babies delivered by the two methods The fœtal loss rate in the infants who underwent vaginal delivery is exaggerated by the fact that this was the natural choice in cases where the fœtus was known to have died in the uterus but if we subtract the 8 intra uterine deaths from this group we still find that 4 out of 20 infants died during or after vaginal delivery whereas the fœtal loss in the group of Cæsarean sections was 4 out of 43 I believe that the chief reasons for the reduction in the fœtal mortality rate in our own clinic have been first the wise judgment of the obstetricians in deciding when and how to effect the premature delivery in each individual case and secondly the skill and constant attention of the pædiatricians and nurses who have been responsible for the neonatal care of the babies

Control of Maternal Diabetes

The use of insulin enables us to control the maternal diabetes and to minimise the dangers to the mother but this is not done without much care and several difficulties may be anticipated Pregnancy does not cause a permanent increase in the severity of diabetes but it is common

Duration of Maternal Diabetes

So far as the causes of the fœtal loss are concerned we remain very much in the dark. White herself believes that the duration of the maternal diabetes is of great importance because it is in the long standing case that one is most likely to find arterial disease, and this in its turn is thought to be prejudicial to the placenta. Our figures are again rather small but the duration of the diabetes did not play any part in determining the rate of fœtal loss in this series, and it is noteworthy that the 13 mothers who had been diabetic for more than *ten years did not lose a single baby in late pregnancy or in the neonatal* period. A study of our series has not revealed any single factor which

TABLE VI

Maturity Related to Result of Pregnancy. Abortions Excluded

Duration of Pregnancy at Delivery Weeks.	Result of Pregnancy				Total Fœtal Loss.	Total Pregnancies
	Intra Uterine Death.	Stillbirth.	Neonatal Death	Live Birth.		
30	0	1	1	0	2	2
31	0	0	0	0	0	0
32	0	0	0	1	0	1
33	1	0	0	0	1	1
34	0	0	0	2	0	2
35	[illegible]	0	0	4	[illegible]	6
36	2	1	2	19	5	24
37	2	0	1	16	3	19
38	1	0	1	9	2	11
39	0	0	0	2	0	2
40	1	0	0	1	1	2
41	0	0	0	1	0	1
Totals	9	2	5	55	16	71

may be said to play an important part in the causation of fœtal loss other than those which have already been discussed.

Early Delivery

In the prevention of infant death we have already seen that early delivery has an important place because it reduces the incidence of stillbirth. But this practice has been extended in an attempt to lower the incidence of intra uterine death which occurs most often after the thirty fifth week. As a result the obstetrician is faced with the difficult problem of judging the most suitable time for the delivery. This must be early enough to minimise the risk of intra uterine death and yet not so early as to jeopardise the child's survival on account of undue prematurity. Table VI emphasises the difficulty of this decision for it shows that 3 intra uterine deaths occurred in or before the thirty fifth week, though it is true that in the case of the one in the thirty third week the fœtus was anencephalic and thus beyond help. Sixty out

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to observe a rise in the insulin requirements during the second and third trimesters and the dose of insulin may have to be doubled during the course of the pregnancy Diabetics are not immune to the fall in the renal threshold for glucose which is common during pregnancy When this fall occurs it is impossible to judge the insulin requirement without estimating the blood sugar, for attempts to obtain freedom from glycosuria usually lead to the development of hypoglycæmia In some cases pregnancy causes the diabetes to become unstable and it is difficult to prevent the patient oscillating between ketosis and hypoglycæmia Under these circumstances success depends upon close supervision and we see our patients at weekly intervals and encourage them to report any difficulty immediately without waiting for their next appointment If they are particularly difficult to stabilise we admit them to hospital without delay On the day of delivery special problems are encountered and I have already described how the dangers of hypoglycæmia are anticipated by a reduction in the dose of insulin but during labour it may also be necessary to insist that the patient takes small feeds of carbohydrate At this time too the key to success lies in frequent observation of the patient and the physician must be prepared to give freely of his time

Conclusions

Although we may be allowed to feel a modicum of satisfaction that the outlook for the fœtus has improved to a considerable extent, we must not remain blind to the fact that this improvement has been achieved by the adoption of the basically unsatisfactory procedure of premature delivery and we must not rest until we have learned how to prevent intra uterine death and overgrowth of the fœtus so that the diabetic mother may carry her baby to term and be delivered in the normal manner without prejudice to the life of her infant

Finally it must be remembered that a study of the pregnant diabetic can teach us much about the disease itself For example we have learned that clinical diabetes is only a late stage in an abnormal process which may begin many years before the disease is recognisable As yet the significance of this discovery is only vaguely appreciated and in fact there is little knowledge of how the pre diabetic woman and far less the pre diabetic man may be recognised with any certainty None theless it is of vital importance that we should learn how to make a confident diagnosis of the pre diabetic state not only so that the pre diabetic fœtal loss rate may be reduced by the application of the methods which have proved of value in the diabetic pregnancy but also because if we are ever able to prevent the onset of diabetes we must be in a position to recognise those who are destined to develop the disease

I am much indebted to the Obstetricians of the Simpson Memorial Maternity Pavilion for permission to make use of their cases and for their encouragement I am particularly grateful to Professor D M Dunlop for his advice and support

We are faced therefore, with two conflicting impressions On the one hand there is the idea that the thereapeutic agents now available especially the antibiotics penicillin aureomycin streptomycin and chloramphenicol are so powerful so entirely adequate to meet every need that the complete elimination of V D if not exactly in sight is at any rate just over the horizon The inescapable corollary to this idea is that the venereologist of the future will become a back number something which the progress of medical science has rendered no longer really necessary something outmoded and discardable

The contrasting idea emphasises that modern treatment even at its best has not proved completely adequate and may even conduce to a spreading of venereal disease that in fact the present state of affairs has produced many difficult problems and certainly does not seem to warrant any assumption that the venereologist is likely soon to become redundant A careful examination of the present position of the main venereal diseases should enable a prediction of what the future is likely to hold and may indicate an answer to the question Whither venereology?

In spite of recent advances in prophylactic technique syphilis still (1950) remains a prevalent disease During the four immediate post war years of 1946 47 48 and 49 the Edinburgh clinics alone received 3911 cases of which 2869 were new fresh infections and 1042 transferred in *i e* syphilis under treatment For the whole of Scotland the cases of syphilis in the four post war years aggregated 12 182 and comprised in the successive years 1946 47 48 and 49 3913 3277 2760 2232 These numbers reflect the usual increase in incidence brought about by mobilisation and demobilisation and the general lowering of moral values consequent upon a world war They afford an impressive testimony to the prevalence of promiscuity and the high infectivity of syphilis which has continued to spread widely in spite of the fact that young adults serving in the armed forces of the various combatant nations received carefully thought out instruction in how to avoid becoming infected with venereal disease Cinema films were used to popularise this instruction and condoms and prophylactic packets were issued on a stupendous well nigh incredible scale In the American forces serological tests for syphilis were carried out routinely on entry into and release from the various services Yet still syphilis has continued to spread

The first thing requiring emphasis in syphilology to day is the continued importance of and necessity for the invariable routine employment of the full diagnostic procedure This procedure should include the examining of serum from genital lesions of any and every sort the serum to be expressed or extracted from any suspicious abraded or indurated area or enlarged lymphatic gland and searched diligently for spirochæta pallida by dark ground illumination Repeated and persistent searching for the treponemata should be associated with repeated and continued examination of the blood by the Wassermann

RECENT DEVELOPMENTS IN VENEREOLOGY

By R C L BATCHELOR

EVENTS have marched very rapidly since the introduction of the sulphonamides in 1935 and of penicillin in 1943 Indeed the advance has been so rapid as to raise the question, ' Are we heading towards the complete eradication of venereal disease ? " That this question is not merely a hypothetical one is indicated by a recent paragraph in the *Lancet* which tells of an attempt to be made to eradicate V D in the island of Haiti, the method suggested apparently being the injection of penicillin into the whole population

Contrasted with this optimistic outlook is the much less comfortable *reflection that penicillin does not cure 100 per cent even of gonorrhœa,* but may merely by the suppression of symptoms, produce an illusory impression of cure and that the uncured residue will form a reservoir of infection and spread the disease This danger has been exemplified by a recent analysis of a series of cases published by King and his colleagues (*Lancet*) Moreover, the method of cure does not confer any immunity, and is nowadays so short and simple that the patient is deceived into regarding his infection either with gonorrhœa or with syphilis as a relatively trivial incident The lessening of a sense of *seriousness in the patient s mental assessment of the whole circum* stances will inevitably lead to a lessening also of his sense of respon sibility These dangers are well voiced and summarised in a lecture delivered recently by John H Stokes on ' The Modern Venereal Disease Problem ' Stokes adduces as one of the influences favouring promiscuity the successes and advances of modern treatment ' and specifies as items in this factor—

(*a*) ' The myth of the miracle drug with the 100 per cent cure
(*b*) The breaking of rapport with the patient
(*c*) Cure without discomfort or inconvenience or loss of time
(*d*) Cure at State expense

As a further factor favouring promiscuity, the cause of V D Stokes contrasts " The failure of modern treatment and analyses this failure as *including*

" (*a*) The non cure margin of 4 to 30 per cent
(*b*) Cure without immunity
(*c*) Cure without responsibility

Stokes expresses the possibility that modern treatment spreads disease and states that this is the gravest and most unanswerable paradox in the physician s and the health worker s field to-day '

Read 11th May 1950

the original 40 000 units to 100 000 or even 200 000 units while maintaining the time interval between the doses at three hours or even reducing it to two hours Instead of the original yellow amorphous penicillin pure white crystalline penicillin G is now readily available and in general use

The question of the optimum duration of treatment has been the subject of considerable study and debate The results of two American nation wide studies tended to show that when penicillin was used alone the length of the course of treatment should not be less than fifteen days On the other hand Mahoney and his colleagues have been devoting their attention to the possibility of developing a therapy of less than seven or eight days duration and in particular have been investigating the practicability of devising a single injection repository vehicle therapy for early syphilis With a suspension of procaine penicillin in oil (1 c c = 300 000 units) in which is incorporated 2 per cent of aluminium monostearate a dose of only 1 c c will produce therapeutic serum levels for at least forty eight hours and on an average for more than twice that time When the dose is increased to 2 c c or 3 c c the effective blood levels are further prolonged There is experimental evidence to indicate that a maintained therapy lasting seventy two hours is likely to be highly effective All this goes to show that Ehrlich's silver bullet his therapia magna sterilisans which would wipe out syphilis at one blow if not actually in our hands is at any rate very nearly within reach

The other side of the picture in syphilotherapy shows that in Britain the majority of clinicians still prefer to use both arsenic and bismuth in addition to penicillin In at least one clinic the use of arsenicals has been abandoned and reliance is placed on penicillin plus bismuth In the U S A there is still a strong body of opinion (notably the workers in the Chicago Intensive Treatment Centre) in favour of a combination of all the proved therapeutic agents fever arsenic bismuth and penicillin in a treatment period compressed into thirty hours This group believes and presents evidence to show that all these agents act synergistically They maintain that their method permits of the effective treatment of early infectious syphilis in less than a day and a half with a failure rate at the end of twelve to fifteen months observation of only 13 per cent The claim is made that no serious reactions occurred yet more than half of the patients did have reactions especially gastrointestinal disturbances and derangements of the kidneys and liver Intensive treatment centres have not been established in this country and there must be few clinics using fever extensively in the treatment of early syphilis

A noteworthy trend in Britain has been seen in the choice of arsenicals in the form of a swing away from mapharside in favour of the older drug neoarsphenamine *i e* N A B or its congeners Many clinicians feel that mapharside is excreted so quickly that it must be given at least twice or even thrice a week whereas neoarsphenamine is effective

and Kahn tests Insistence on adequate diagnostic procedure in every case is especially demanded to day because penicillin is so frequently used either for the prophylaxis of syphilis itself or for the prophylaxis or treatment of a gonorrhœa with which a superimposed syphilis may be a concomitant

Penicillin used in the prophylaxis of V D may be given orally or by injection The oral method, which is usually aimed at the prevention of gonorrhœa, consists in the administration of tablets of oral penicillin G each tablet containing 100 000 units An effective dose would be at least 200 000 units and preferably 500 000 units This oral prophylaxis has been used to reduce the incidence of gonorrhœa among Navy personnel going on shore leave in areas of high prevalence The method involves the risk of modifying the usual course and progress of an incubating concomitant syphilis for example there may appear on the penis an erosion which yields only negative dark fields and which may heal quickly and spontaneously while at the same time the appearance of positivity in the Wassermann and Kahn tests may be delayed

The parenteral method of prophylaxis or abortive treatment which has been used against syphilis employs 600 000 units of penicillin in peanut oil and beeswax This method has been employed to prevent the disease developing in contacts of known cases of early infectious syphilis

Only time will tell what degree of success will attend this technique but in the meantime an obvious precaution will be the insistence on a follow up of serological tests taken at intervals over a sufficiently long period of not less than six months and preferably one year with at least one testing of the cerebrospinal fluid

In the treatment of established syphilis the chief point at issue at the present time is whether penicillin used alone in single or multiple courses constitutes the best treatment or whether penicillin should be combined with adjuvants such as the traditional arsenicals and bismuth or used in conjunction with one of the newer antibiotics especially aureomycin

The various points in the case for and against penicillin used alone without adjuvants are first it may now be taken as definitely established that penicillin alone can cure syphilis After six years of observation of the first four patients treated for syphilis by Mahoney and his colleagues in 1943 three have remained clinically and serologically negative and the fourth after a considerable period of negativity got a reinfection (Incidentally this patient a Negro male 18 years old seems to have had boundless confidence in modern treatment because it is recorded that while under observation he had thirteen gonorrhœal infections within less than a year—surely an outstanding example of cure without immunity and cure without responsibility!) These early successes were confirmed by subsequent reports and the results achieved improved steadily as experience was gained Using aqueous penicillin the tendency has been to increase the individual dose from

cent The success achieved with P A M (i e procaine penicillin in oil with aluminium monostearate) is even more remarkable The preliminary figures after fifteen months post treatment observation suggest that one two or four injections of P A M in dosage of 2 4 to 4 8 mega units yields results which compare favourably with those from a similar dosage of aqueous penicillin given in ninety two-hourly injections over a period of eight days This finding if confirmed seems likely to inaugurate a complete change and readjustment in the treatment of syphilis throughout the world The foundations of the old traditional syphilo therapy are rocking under the impact of P A M and this lively newcomer is making a bold bid to supplant P O B as an aspirant to the throne Some time ago the rumour of a one shot cure' for syphilis started to spread around and was received for the most part with frank incredulity But now the vision has taken definite shape and it certainly seems to be something quite substantial

The newer antibiotics streptomycin aureomycin and chloram phenicol have all been tried out against the spirochæta pallida and aureomycin and chloramphenicol have been proved to be active Because intramuscular injections cause severe pain aureomycin is given by the mouth in capsules containing 250 mg The individual dose is from two to four capsules (0 5 to 1 gm) and this is given six hourly making 2 4 gm per day The disappearance of spiro pallida from chancres and secondary papules and the healing of these lesions while slower than with penicillin is progressive and fairly rapid The total amount necessary for complete cure has not been definitely determined and the necessity for regular swallowing of the drug continued for many days would tend to make the treatment too dependent upon the co-operation of the patient Toxic action upon the gastro intestinal tract is frequent especially diarrhœa but usually not severe

Chloramphenicol is also given by mouth in capsules of 250 mg every six hours The effective individual dose in syphilis is 1 gm (four capsules) and this is repeated six hourly making 4 gm per day for about ten days to a total dosage of 40 gm The toxic effects are stomatitis and diarrhœa The rate of disappearance of spiro pallida and the healing of lesions is again slower than with penicillin As compared with injections the absorption from the oral administration obligatory with chloramphenicol and aureomycin is less certain and less reliable and neither of these drugs can compete with penicillin in syphilotherapy

GONORRHŒA

With the almost universal adoption of penicillin therapy the impression seems to be gaining ground that gonorrhœa has been debunked and has fallen in estimation as a disease of serious significance The prevalent idea is that penicillin has got gonorrhœa in the bag but perhaps the bag has a hole in it like the legendary bag that held

when given only once a week, thereby saving the time of both patient and doctor On the other hand mapharside undoubtedly has fewer and slighter toxic effects than its rival

At the present time most of the indications point to penicillin used alone as the likely choice in the future, and indeed there are many outstanding advantages which can be adduced in justification Penicillin is essentially non toxic and the urticaria which it sometimes causes can usually be controlled or modified by antihistamine drugs Already papers have been published showing excellent results in the treatment of primary and secondary syphilis from the use of single injections of from 1 2 to 2 4 mega units of procaine penicillin in oil with 2 per cent of aluminium monostearate Estimation of blood concentrations has shown that the 1 2 mega unit dose of this repository preparation maintains blood levels above the hypothetical minimum therapeutic concentration of 0 03 units per c c of serum for over seven days This observation on the maintenance of effective blood levels for over a week from a dose of 1 2 mega units (4 c c of the suspension) suggests the practicability of adequately treating early syphilis by a single injection of 4 c c once a week for four weeks In order to guard against the possibility of individual variations in blood concentration the frequency of administration of the 1 2 mega unit dose could be increased to twice weekly for four weeks giving a total dosage of 9 6 mega units One of the modern preparations of oil suspended procaine penicillin (Prolopen) actually carries in each c c 100 000 units of soluble penicillin G in addition to the 300 000 units of procaine penicillin, so that by choosing this preparation the total penicillin in the four weeks course would be increased to 10 4 mega units This four weeks course of twice weekly repository penicillin for early syphilis will be given a trial in the Edinburgh clinic

In assessing the efficacy of penicillin in early syphilis due allowance must be made for the fact that the yellow amorphous penicillin used from 1943 to about the summer of 1946 varied in the relative proportion of the fractions G F X and K and in potency measured in units per milligram was therefore unreliable and gave a false impression of the real value of penicillin as the failure rates accruing from it were variable and sometimes disappointingly high The introduction and adoption in practice of pure white crystalline penicillin G has been followed by a remarkable lowering of the reported failure rates The June 1949 Progress Report issued by the Medical Director of V D of the U S Public Health Service analysing the records of 5400 patients treated solely with crystalline penicillin G administered in aqueous solution or peanut oil and beeswax with total dosages of not less than 2 4 mega units estimates the failure rates for early syphilis as 2 3 per cent for seronegative primary syphilis 6 2 per cent for seropositive primary syphilis and 12 per cent for secondary syphilis This recent analysis creates a very different and much more favourable impression than the earlier reports with failure rates running up to 25 or 30 per

cent The success achieved with P A M (*i e* procaine penicillin in oil with aluminium monostearate) is even more remarkable The pre liminary figures after fifteen months post treatment observation suggest that one two or four injections of P A M in dosage of 2 4 to 4 8 mega units yields results which compare favourably with those from a similar dosage of aqueous penicillin given in ninety two hourly injections over a period of eight days This finding, if confirmed seems likely to inaugurate a complete change and readjustment in the treatment of syphilis throughout the world The foundations of the old traditional syphilo therapy are rocking under the impact of P A M and this lively newcomer is making a bold bid to supplant P O B as an aspirant to the throne Some time ago the rumour of a one shot cure for syphilis started to spread around and was received for the most part with frank incredulity But now the vision has taken definite shape and it certainly seems to be something quite substantial

The newer antibiotics streptomycin aureomycin and chloram phenicol have all been tried out against the spirochæta pallida, and aureomycin and chloramphenicol have been proved to be active Because intramuscular injections cause severe pain aureomycin is given by the mouth in capsules containing 250 mg The individual dose is from two to four capsules (0 5 to 1 gm) and this is given six hourly making 2 4 gm per day The disappearance of spiro pallida from chancres and secondary papules and the healing of these lesions while slower than with penicillin is progressive and fairly rapid The total amount necessary for complete cure has not been definitely determined, and the necessity for regular swallowing of the drug continued for many days would tend to make the treatment too dependent upon the co operation of the patient Toxic action upon the gastro intestinal tract is frequent especially diarrhœa but usually not severe

Chloramphenicol is also given by mouth in capsules of 250 mg every six hours The effective individual dose in syphilis is 1 gm (four capsules) and this is repeated six hourly making 4 gm per day for about ten days to a total dosage of 40 gm The toxic effects are stomatitis and diarrhœa The rate of disappearance of spiro pallida and the healing of lesions is *again slower than with penicillin* As compared with injections the absorption from the oral administration obligatory with chloramphenicol and aureomycin is less certain and less reliable and neither of these drugs can compete with penicillin in syphilotherapy

GONORRHŒA

With the almost universal adoption of penicillin therapy the impres sion seems to be gaining ground that gonorrhœa has been debunked and has fallen in estimation as a disease of serious significance The prevalent idea is that penicillin has got gonorrhœa in the bag but perhaps the bag has a hole in it like the legendary bag that held

or didn't hold the fox This prevalent idea of the all sufficiency of penicillin needs examination

A common history of a case of urethritis coming to a clinic is that first of all he had injections of penicillin next he had a course or courses of sulphonamides and then because his discharge still kept running he is sent to the clinic The first problem posed by these cases is the one of diagnosis Most often no attempt at diagnosis has been made no smears taken A purulent discharge pain on passing water signs of inflammation it looks like gonorrhœa time presses penicillin is handy, better have a shot of it just in case! But non gonococcal urethritis is just as common as gonorrhœa and the cart before the horse method of treatment before diagnosis confuses the issue more than some what It still is clear we need a smear and in any case of doubt a culture helps you out

Fortunately true penicillin resistance in authentic gonococcal infections, if it does really occur must be comparatively rare The usual treatment for an uncomplicated gonorrhœa in a man is one injection of 300 000 units of procaine penicillin in oil with aluminium monostearate and this same injection may be repeated in twenty four hours time Most of the 5 per cent or so of failures will respond to a repetition of the same treatment

Cases of gonorrhœa with complications such as prostatitis and epididymitis are best taken into hospital and may be successfully treated with multiple injections of aqueous penicillin 100 000 units three hourly for from three to six days according to the clinical response

A recent gonococcal infection may be superimposed on a stricture or other chronic urinary infection with B coli or streptococci Streptomycin may be useful in such cases given intramuscularly in ¼ gm doses six hourly for five to six days Streptomycin can deal effectively with the gonococci as well as with the secondary organisms and may be exhibited from the beginning or kept in reserve for use after an initial attack with penicillin

Non gonococcal urethritis affords good exercise for clinical acumen Unless sulphonamide or penicillin sensitive organisms such as streptococci are present in the smears and cultures sulphonamides such as sulphadiazine or sulphathiazole or penicillin are likely to be of little value When the smears contain only pus cells and no organisms and the inflammation involves the posterior urethra and the bladder some of these cases will respond like magic to three or four small (0 3 gm) doses of N A B intravenously at intervals of three days However, the proportion of cases which do so respond is unfortunately small Those which do clear up on N A B are classed as abacterial pyuria for want of a better name

In Reiter s syndrome an abacterial urethritis is associated with eye inflammations such as conjunctivitis and iritis and also with arthritis of several joints and hyperkeratotic skin eruptions on the glans penis soles and elsewhere This peculiar condition is highly resistant to many

of the usual methods of treatment and in particular is not favourably influenced either by sulphonamides or by penicillin Fever therapy induced by the inductotherm cabinet or by intravenous T A B vaccine is usually very helpful and injections of streptomycin 0 5 gm six hourly are of value in some cases

Nearly all the victims of Reiter s disease are men and an abnoxious characteristic is that attacks may keep on recurring over many years Meanwhile the wives of the patients appear to remain immune

A feature of present day venereology is the recent tremendous strengthening of therapy by the introduction of new antibiotics Lymphogranuloma inguinale (or lymphogranuloma venereum as it is called in the U S A) is a rare visitor here in Scotland but is common in the U S A and in the Far East Occasionally a case turns up where the inguinal glands are swollen and hard with purple discolouration of the overlying skin and sinuses may have formed An intracutaneous Frei test with Lygranum antigen may prove the diagnosis Intensive sulphadiazine therapy potentiated by fever from intravenous T A B vaccine or the inductotherm cabinet will remain the first resource owing to the high price of aureomycin but it is comforting to know that aureomycin is available for the more advanced cases with multiple sinuses and inflammatory strictures of the rectum These advanced cases were formerly most resistant and intractable and even with aureomycin treatment for one to two months and a total dose of 50 to 100 gm may be necessary Aureomycin is unique in that it is the first agent to prove potent in all the five chief venereal diseases namely syphilis gonorrhœa chancroid L G I and the Leishmania granuloma inguinale

Chancroid usually succumbs easily to sulphadiazine or sulphathiazole but where a patient is sulphonamide sensitive or the disease sulphonamide resistant streptomycin may be used and is generally effective Aureomycin and chloramphenicol (chloromycetin) are also of value in chancroid and could be exhibited by the usual oral route in any case not making satisfactory progress under parenteral streptomycin Chancroid yields to quite small doses of aureomycin one capsule of 250 mg four times daily for five days (*i e* 1 gm per day and a total dose of 5 gm) is sufficient

In certain cases there may be indications for oral in preference to parenteral administration Gonorrhœa can be cured by oral penicillin as was shown recently in Edinburgh by Horne who used two doses each of 500 000 units (five tablets of 100 000 units) the second dose given at an interval of three to six hours after the first

The other two orally administered antibiotics aureomycin and chloramphenicol (chloromycetin) can also be used to treat gonorrhœa In the case of aureomycin three doses each of 1 gm will suffice When chloramphenicol is used a dosage of 1 gm thrice daily for two days is satisfactory Chloramphenicol is less toxic than aureomycin with the latter nausea vomiting and diarrhœa are common At

present the use of these newer agents is restricted by the scantiness of supplies and the greatness of the cost

In conclusion it may surely be claimed that the future for venereology seems bright with promise Specific and effective remedies are now available for the five common venereal diseases, viz syphilis gonorrhœa chancroid L G I and granuloma inguinale Non gonococcal urethritis still poses a problem but the solution of this problem may be steadily brought nearer as the electron microscope enlarges our knowledge of viruses and similar minute bodies With the agents already in our hands, attractive possibilities are open The certain cure of syphilis in pregnancy, the almost complete eradication of pre natal syphilis saving the life of the congenital infant, abolishing blindness and deafness in the older child preventing insanity from G P I—all these are now more than possibilities The patient s burden has been lessened enormously in time saved pain avoided and mental distress alleviated

The lecture was illustrated by lantern slides showing the different manifestations of the venereal diseases for which penicillin and the newer antibiotics are used and showing also the different features of Reiter's disease

CONTRACTED PELVIS

By ROBERT BROWN M B CH B M R C O G

CONTRACTED pelvis has for many years been recognised as the commonest cause of dystocia Its incidence does vary greatly in different areas and it would serve no useful purpose to compare a large series of cases from the literature It is of interest however to compare the incidence in this area with that of the only other large Scottish town McLennan (1944) gave the hospital incidence in Glasgow as 15 per cent the Edinburgh figure for the same period being under 3 per cent

I would like to emphasise here that I chose the title of ' Contracted Pelvis rather than disproportion because while disproportion is not always found in cases of contracted pelvis true disproportion is rare if the pelvis is normal This was brought most strongly to my notice while helping to prepare a paper on Cæsarean section for the decade 1940-49 This paper which was presented to the Edinburgh Obstetrical Society in January of this year by the obstetrical registrars of this region showed very plainly that many women on whom elective Cæsarean sections were performed for alleged disproportion were able to deliver themselves subsequently of larger babies by the vaginal route As it was impossible to separate the cases of disproportion from those of contracted pelvis in this decade I thought it would be of interest to investigate the incidence method of delivery and results in a series of proved cases of contracted pelvis I have taken the figures from the Simpson Maternity Pavilion for the years 1950 and 1951 to form the basis of my paper I would like to take this opportunity to thank the Chiefs of the Simpson for the use of their cases the Department of Obstetrics for the slides and not by any means least my fellow Registrars for permission to quote from the January paper which has not yet been published

There has been a tendency to minimise the mechanical side of labour in favour of the functional but in every patient approaching term the accoucheur must ask himself is the pelvis adequate? If not he should attempt to find out exactly where the abnormality lies because although we are dealing usually with full term healthy babies

Read 18th June 1953

and relatı\elỳ normal mothers the results ın the past ha\e been poor and stıll are far from perfect

In order to apprecıate the ad\ances made ın the treatment of contracted pel\ıs ın the last quarter centurv I ha\e perused the records of the Edınburgh Ro\al Maternıt\ Hospıtal and ıts successor the Sımpson Memorıal Maternıt\ Pa\ılıon for the \ears 192, 49 I ha\e dıvıded the results ınto five \ear perıods and ın Table I one can obtaın

TABLE I

Contracted Pelvıs ın Fıve Year Perıods

	1925 9	930-34	193 39	940-44	1945 49	95 –
Total contracted pelvıs	408	367	25,	307	469	400
Maternal deaths	19	10	2	4	0	0
Perınatal mortalıty	-0	63	57	34	26	55
Spontaneous delıvery	50	89	51	7-	116	159
Forceps delıvery	66	66	6,	56	81	75
Induction of premature labour	90	8-	3,	23	-	0
Cæsarean section (total)	18	161	128	164	26,	16,
Cæsarean section (prıms)	60	46	48	89	153	52
Craniotomy	16	17	15	13	3	2
Version+breech extraction	4	6	0	1	0	0
Total delıvery after 28 weeks	8341	9620	10 623	14 118	15 536	14,000
Per cent. of contracted pelvıs	4·9	3·9	2 4	2 1	2·9	8,

an o\erall pıcture durıng thıs tıme The column on the extreme rıght ıs an estımated figure for the fi\e \ear perıod from 1950 onwards constructed by takıng the figures for the last three \ears and brıngıng them up to the same le\el as the other columns Its value ıs merel\ to show the current trend ın the treatment and the results therefrom The maın poınts to be noted from the table are the dramatıc fall ın the maternal mortalıt\ whıch sho\s that as far as lıfe ıs concerned both vagınal delı\er\ and Cæsarean sectıon are now relatı\el\ safe The perınatal death rate b\ \hıch I mean combıned stıllbırth and neonatal deaths whıle a great ımpro\ement ıs stıll too hıgh for \hat ıs usually a normal baby

Regardıng the varıous methods of delı\ery probabl\ the most marked change ıs the almost complete dısappearance of ınductıon of premature labour Thıs \as as a rule undertaken ın the hope of a\oıdıng Cæsarean sectıon but \hıle possıbl\ the mother was at less rısk the unborn chıld \as subjected to all the complıcatıons of premature labour often prolonged and requırıng an ınstrumental *delı\ery Versıon and breech extractıon ha\e been condemned ın the* treatment of contracted pelvıs for many \ears but ın the pre antıbıotıc da\s \as a lıfe sa\ıng measure for the mother ın ınfected cases admıtted late ın labour Lıke cranıotom\ \hıch ıs no\ada\s onl\ done ın a morıbund or dead fœtus ıts ıncıdence ıs very lo\

Cæsarean sectıon \as e\en ın the first fi\e \ear perıod the maın lıne of treatment generallv electı\e and usually of classıcal type The ıncıdence of Cæsarean sectıon appears to ha\e rısen ın the perıod

1945 49 but in this period the total number of births rose very markedly, and one can see that the total number of cases of contracted pelvis also was correspondingly high

I think that this is an appropriate moment to describe a few basic facts The definition of contracted pelvis as given by Litzmann is still as good to day as when first written in 1861 *i e* A contracted pelvis is one in which one or more diameters are so shortened that this may interfere with the normal mechanism of labour

The pelvic brim is known to all as the inlet to the true pelvis but the actual measurement of the obstetrical conjugate varies from text book to text book Johnstone and Kellar (1952) give the measurement as 4¼ 4½ in (10 8 11 4 cm) Eden and Holland (1948) as 4⅜ in (11 cm) Smout as 4½ in (11 2 cm) and De Lee and Greenhill (1947) 4⅜ in (11 cm) It should be pointed out however that the available con jugate is the most important measurement, and is defined as reaching from the upper margin of the posterior surface of the symphysis pubis to the nearest point on the sacrum For the purpose of this paper I have taken the figure of 4 in (10 1 cm) as the lower limit of normal for the available conjugate

According to the above-named authors the normal measurement of the transverse of the brim is 5 5¼ in (12 7 13 3 cm) This measure ment is as a rule adequate but in anthropoid pelves is less than the true conjugate yet there is no real pelvic contraction However should this measurement be less than 4½ in (11 2 cm) one must ascertain that there is adequate compensation in the antero posterior lest one is faced with a case of generally contracted pelvis the most treacherous type of all

The cavity of the pelvis is generally the largest part and except when there is a convex sacrum difficulty is rarely encountered here

Turning now to the pelvic outlet there is a great deal of controversy as to just exactly which measurements really are important I have always considered the true bony outlet the plane of least pelvic dimen sions as the important one Its antero posterior is measured from lower end of the symphysis pubis to the tip of the sacrum and the transverse is the distance between the ischial spines The former measurement is 5 in (12 7 cm) according to Johnstone and Kellar while Morris (1947) considers any figure below 4½ in (11 5 cm) as liable to cause difficulty The transverse measurement is usually taken as 4 in (10 1 cm) The only other measurement of any value is the subpubic angle a reduction in which causes a certain amount of waste space at the outlet as the head cannot fit closely under the pubic arch The normal for this is 85 90

Nicholson (1938) and Allen (1947) both discuss the area of the pelvic brim and outlet in assessing the capacity of the pelvis My objection to this is that a very large tran verse cannot compensate for a markedly contracted antero posterior of the brim also the interspinous measurement of the outlet is very variable and one sees a

measurement of 3 in (7 5 cm) not infrequently In spite of this figure causing a small area of measurement vaginal delivery often spontaneous, usually occurred One must assume there is considerable give at the outlet during labour

Before describing the results obtained in the cases under review I thought that it might be interesting to find out if there was any fact which might warn us antenatally of the possibility of contracted pelvis in our patients At the first antenatal visit the height of the pregnant woman is always measured It has been our custom to book all those under 5 ft (1 52 m) in height and on invesitgating a few hundred cases I found that 10 2 per cent were booked for stature alone Turning now to those cases of contracted pelvis who had their height measured I found that 60 per cent were under 5 ft (1 52 m) in height Therefore we can book three fifths of the patients who are likely to have a contracted pelvis at their first antenatal visit Other less reliable signs such as very small hands and feet can also be observed early in pregnancy

A history of such diseases as rickets spinal tuberculosis, congenital dislocation of the hips and poliomyelitis should all warn the obstetrician *of the likelihood of pelvic deformity In this century the number* of motor car accidents has risen markedly and not infrequently the pelvis is involved Irregular healing of the pelvic girdle with excessive callus formation often markedly reduces the size of the pelvic cavity

Previous obstetric history is of great importance and any history of difficult labour in some other hospital should invariably call for a report Even if labour has been spontaneous but fœtal death has resulted a copy of the previous labour record should be obtained A previous Cæsarean section always demands a full investigation especially if the cause was alleged to be contracted pelvis or disproportion A forceps delivery in a primigravida may not infer very much but in a parous woman demands the most thorough investigation Even in cases of proved contracted pelvis forceps were rarely necessary in parous women Just because a woman has had one or more spontaneous vaginal deliveries does not mean that the pelvis is normal a bigger baby may well cause dystocia A new parous patient should merit as much if not more assessment than a primigravida I would like to mention one recent case that came under our care and is in fact one of this series Mrs S was a para 16 all spontaneous deliveries but on investigating the history further it was found that 6 babies had died at or shortly after birth A vaginal examination showed that the pelvis was markedly reduced in size and X ray pelvimetry confirmed the available conjugate to be 3 6 in (9 cm) As well as emphasising the value of a thorough check up in a parous woman this case illustrates most vividly the fact that any stillbirth even in a spontaneous delivery should be followed up in search of maternal as well as fœtal abnormality Finally if one has a difficult delivery it should be investigated before the patient leaves hospital If any

permanent abnormality is found the patient should be told to return if another pregnancy occurs The investigation will always be available should she go to another area in a subsequent labour

Nowhere is the previous history of more importance than in the woman with contracted pelvis The 86 parous women in my series had a total of 162 children of whom 35 were lost at or soon after birth This figure of over 20 per cent combined stillbirth and neonatal mortality in babies nearly always mature and normally formed demands further study Table II shows the previous fœtal loss in those cases

TABLE II

Previous History of Women with Contracted Pelvis

Present Mode of Delivery	Previous Mode of Delivery	Total Babies	Stillbirth and Neonatal Deaths.
	5 Cæsarean × 1	5	1
	1 Cæsarean × 2	2	0
39 Vaginal	7 { Cæsarean +	7	1
	vaginal	8	3
	6 Vaginal	4	6
		Total 64	Total 11
	19 Cæsarean × 1	19	1
	10 Cæsarean × 2	0	1
47 Cæsarean section	8 { Vaginal +	14	9
	Cæsarean	10	0
	10 Vaginal	35	13
		Total 98	Total 24

delivered vaginally in the present pregnancy to be much lower than in those having Cæsarean section Furthermore one can see that by far the highest fœtal loss is in those cases in whom vaginal delivery was followed by Cæsarean section The figures imply that the fœtal loss of over 60 per cent forced the obstetrician to choose the alternative method of delivery The last column is of interest in that in spite of having had an average of over 3 babies vaginally a Cæsarean section was ultimately necessary usually because of the increased size of the child

At the thirty sixth week of pregnancy it is the normal practice to estimate the pelvis clinically The whole pelvic outlet can be palpated easily and a rough idea obtained as to whether it is contracted or not Unless the head is engaged one should always attempt to measure the diagonal conjugate As a rule one fails to reach the promontory of the sacrum in a normal pelvis but whether one always reaches it in a contracted pelvis seemed worth investigating To my surprise I found that in only 50 per cent of those cases of contracted pelvis in whom internal pelvimetry was undertaken was the promontory of the sacrum reached Most of these were in the lesser degree of contracted pelvis admittedly but to my mind there is another explanation In

many cases of contracted pelvis there is a high inclination of the pelvic brim and in performing internal pelvimetry one tends to reach too far down The only method of finding out this angle for certain is by X ray, and I am convinced that one of the commonest causes of high free head late in pregnancy, and also of alleged disproportion in the normal pelvis is a highly inclined pelvis The normal inclination is 55° to the horizontal but it may increase to 90° in some cases

If vaginal examination is only successful in finding half of the cases of contracted pelvis how else can they be diagnosed? The high free head in the primigravida in the last month of pregnancy always demands attention If one cannot make it engage by one of the standard manœuvres such as Muller s, as modified by Munro Kerr, a full clinical and X ray investigation should be undertaken A

TABLE III

Types of Contracted Pelvis and Methods of Delivery

Type	Total	Cæsarean Section	Forceps Delivery	Spontaneous Delivery	Other
Flat pelvis	122	48	20	53	1
Justo minor	12	9	2	1	
Oblique contraction	4	4			
Outlet contraction	22	7	9	5	1
Total	160	68	31	59	

breech presentation in either primigravid or parous women also demands a full investigation with X ray pelvimetry Other malpresentations are rare although a shoulder presentation is occasionally found ante natally It is of interest that of the 160 cases of contracted pelvis only 10 had malpresentations 8 breech and one each of brow and transverse lie

Turning our attention now to the type of pelvis found in the 100 women Table III shows that by far the commonest type of contraction was flat pelvis Flat pelvis is of two types rickety flat and simple flat and it would have been of interest to give the incidence of each type Unfortunately this was impossible as some of the records especially in the parous women were incomplete but leaving these out I would estimate that rickety flat was three times the more common variety

The justo minor type of pelvis was less common than I would have thought but nevertheless is the most potentially dangerous in practice as it is often not recognised till late in labour when the head is excessively moulded into the pelvis

Outlet contraction with a normal brim was diagnosed in 22 cases generally because of difficulty at delivery As a matter of fact elective Cæsarean section was carried out in 4 cases in subsequent pregnancies because of this diagnosis no doubt because the fœtal loss had been high previously The 4 cases of obliquity of the pelvis all occurred in

patients with permanent deformity such as congenital dislocation of the hips and poliomyelitis

What were the methods of delivery undertaken in these 160 women? Table IV shows how the 74 primigravidæ and the 86 multiparæ were delivered and the results to the babies As the problem is rather different in primigravid than parous women I have analysed the results separately In the primigravidæ there were 21 Cæsarean section 9 of these being operations of election Five had prolonged labours the reason for operation being disordered uterine action rather than disproportion alone The remaining 7 cases had Cæsarean section for what one might call a failed trial of labour The duration

TABLE IV

Type of Delivery and Perinatal Loss

Delivery	Cæsarean Section	Forceps Delivery	Spontaneous Delivery	Craniotomy	Breech Extraction
PRIMIGRAVIDA					
Numbers	21	26	5	1 (F F O)	1 (Twins)
Perinatal Mortality S B	0	1 (Cerebral hæmorrhage)	0	1	1 (Cerebral hæmorrhage)
Perinatal Mortality N N D	2 {1 Spina Bifida, 1 Asphyxia}	0	0	0	1 (Cerebral hæmorrhage)
PAROUS					
Numbers	47	5	34	0	0
Perinatal Mortality S B	3 {1 Cerebral hæmorrhage, Asphyxia}	1 (Cerebral hæmorrhage)	2 {1 Hydrops, 1 I U D}	0	0
Perinatal Mortality N N D	2 {1 Premature, 1 Icterus gravis}	0	0	0	0

of labour in these women varied from seventy one to twenty two hours, and the cervical dilatation from a tip to full dilatation Possibly in some of these the trial of labour was rather inadequate No babies were stillborn in this group but there were 2 neonatal deaths one from spina bifida the other whose mother was admitted as a case of pro longed labour died of asphyxia the duration of labour being eighty hours

Turning our attention now to vaginal delivery we find that of the total of 53 cases, just under half required a forceps delivery The main reason for forceps delivery was deep transverse arrest of the head with persistent posterior position of the occiput a poor second This is the usual reason for forceps delivery in any series of primigravidæ with normal pelves but the incidence in them is much less

The fœtal mortality in forceps delivery was one stillbirth due to cerebral hæmorrhage and occurred after the use of Kielland s forceps for a high midcavity delivery

Spontaneous delivery was obtained in 25 cases without fœtal loss It is of interest to note that labour was very short in many of these

cases and that it was possible for a 7 lb (3 2 kg) baby to be born spontaneously through an available conjugate of 3 3 in (8 25 cm)

The remaining methods of vaginal delivery were highly lethal to the babies In the one case of breech extraction undertaken in a case of twins both died of cerebral hæmorrhage, one at and one shortly after birth The final case was that of a craniotomy admitted from home after a failed forceps operation The baby was in very poor condition and the mother exhausted so that it was really done as a life saving measure

To sum up the primigravid patients to the 74 mothers were born a total of 77 babies of whom 6 were lost From these one might exclude the congenital abnormality but even although, this leaves a hard core of 6 5 per cent fœtal loss due to contracted pelvis

Considering now the parous women of whom there was a total of 86 we find that more than half had a Cæsarean section Of the 47 of those no less than 39 were elective and 16 patients were sterilised at the same time It is worth noting that most of these women had at least 2 babies before sterilisation but 3 had only had one previous delivery by Cæsarean section I have already mentioned previous history in relation to fœtal loss but I would like to emphasise here that 29 out of 47 of those parous women having a Cæsarean section had had only Cæsarean delivery before The fœtal loss was high in this group 5 babies being lost Three of these occurred in elective operations one from icterus gravis one from prematurity and one from asphyxia In the group in labour 2 failed to survive one because of asphyxia and the other because of cerebral hæmorrhage This last case had previously had an attempted vaginal delivery by high forceps before Cæsarean section was undertaken so possibly it is a trifle unfair to blame it on the abdominal operation I might add that this was the only case of brow presentation in the series

Considering now the cases delivered vaginally one is perhaps surprised to find there were only 5 forceps deliveries in the parous patient It is of interest to note that 2 of these women had never had a vaginal delivery before only one Cæsarean section each One baby was lost the cause being cerebral hæmorrhage in one of the vaginally primiparous patients Finally 34 women had a spontaneous vaginal delivery with the loss of 2 babies In one of these intra uterine death had occurred a week before delivery and in the other the cause was hydrops fœtalis Therefore it can be stated that the method of delivery was not at fault here It should be mentioned here that 7 of these women had previously been delivered by Cæsarean section also 3 of these had never had a vaginal delivery at all

To sum up the results in the parous patients showed a total fœtal loss of 8 babies out of 87 born to 86 women Correcting these for unavoidable fœtal loss we are left with 5 or 6 per cent due to con tracted pelvis This figure is only 0 5 per cent better than for the primigravida and considering that there were twice as many Cæsarean

sections performed in the parous patients, tends to show that Cæsarean section is not the perfect answer to the problem

So far I have considered only fœtal loss we must now consider the results as they affected the mother There were no maternal deaths in the series and only 6 women had morbid puerperia by the Ministry of Health standard Three of these were in each of the Cæsarean and vaginal delivery groups Much more serious than these pyrexial cases which usually settled down rapidly with antibiotics was the maternal catastrophe of rupture of the uterus Only one primigravida had a classical Cæsarean section in the whole series the operation being performed in 1950 The reason given for choosing the classical route was a burn to the lower abdomen As luck would have it she returned in 1951 pregnant again and attended the antenatal clinic regularly She was admitted at the thirty sixth week with signs of impending rupture of the uterus Immediate laparotomy revealed that the classical scar had given way in its whole length but fortunately the baby was still *in utero* and he and his mother survived This case does help to illustrate the danger of classical Cæsarean section and shows that it should be avoided whenever possible especially when further pregnancy is likely

One other case of ruptured uterus occurred in the period under review a previous lower segment Cæsarean section in a first pregnancy which had been followed by a twin vaginal delivery In view of this it was thought possible to attempt to obtain another vaginal delivery although the available conjugate was only 3 6 in (9 cm) After six hours in labour it was apparent that vaginal delivery was unlikely to be easily obtained so arrangements were made to repeat the lower segment operation On opening the abdomen the lower segment scar was found to have ruptured along most of its length however the baby as well as the mother survived This case shows that it is possible to push the attempt to obtain a vaginal delivery too far especially with a fairly marked pelvic contraction and a uterine scar even of lower segment type

One last point concerning the mother must not be forgotten although it was impossible to measure it in the present series I mean the gynæcological legacy of difficult vaginal delivery in contracted pelvis The cases of prolapse third degree tear cervical laceration and permanent pelvic pain are only too common to permit us to forget them for long

From the results obtained in these last two years what lessons are to be learnt in the future management of contracted pelvis? The first essential is early and accurate diagnosis so that adequate arrangements for the delivery can be made I think everyone is agreed that there is only one place for a woman with contracted pelvis in labour—an adequately staffed and equipped maternity hospital As I have already mentioned a great many potential cases of contracted pelvis can be booked at their first antenatal visit merely by measuring the

height The average height of women in Scotland is 5 ft 3 in (1 6 m) so that by booking those under 5 ft (1 52 m) only, we are booking something like 300 women per annum of whom possibly 55 will have a contracted pelvis One might argue that this is wasteful but it must be realised that a great many of these women would be booked for hospital delivery anyway in this area Possibly it is one defect in our present system of booking patients for hospital delivery, that, if they are not accepted at the first antenatal visit they never return unless specially sent back but go elsewhere to search for a bed

I have already mentioned that it is often difficult if not impossible, to reach the promontory of the sacrum in a patient with a high inclination of the pelvic brim even although the pelvis is contracted This is even more difficult in the unco operative patient, and in this type of patient, if the head is high, an X ray picture is invaluable If the head *is high and free within three weeks of term in a primigravid woman* and cannot be made to fit in to the pelvic brim one must make absolutely certain that there is nothing in the pelvis preventing it engaging Fibroids and ovarian cysts are not uncommonly found and for this reason alone I think every patient should have a vaginal examination early in the antenatal period Placenta prævia although uncommon is occasionally a cause of high free head near term If it is suspected of being present soft tissue X rays should be taken with the patient standing Having excluded these one should next make certain that the fœtus is normal The commonest fœtal abnormality preventing engagement of the head is hydrocephalus This is not a common condition but it was shown in our January paper that no less than 11 women had a Cæsarean section for disproportion the babies having hydrocephalus X ray of the fœtus would have prevented some of these but not all as the minor degrees of hydrocephalus are hard to decipher by X ray alone One of the reasons for this is that if the fœtal head is nearer the X ray tube than the pelvis it is magnified on the film If one is not certain if hydrocephalus is present or not it is far better to let the patient go into labour and when the cervix is half dilated palpate the head directly This will often reveal the separated sutures and large fontanelles of hydrocephalus I might add here that before doing a Cæsarean section for any cause whatsoever one should always try to obtain an X ray picture of the whole fœtus It is bad enough for a baby with a congenital abnormality to be born vaginally but to deliver it by elective section is tragic The presence of hydramnios makes *this X ray even more imperative* but as Macafee (1950) has shown an X ray cannot show abnormalities of abdominal or thoracic organs and even minor abnormalities of the spine may not be visible

As I am still on the subject of X rays I think it is an opportune moment to consider X ray pelvimetry This has revolutionised the accurate diagnosis of contracted pelvis because it enables us to use our most highly developed sense To be able to see the whole pelvis

its shape inclination to be able to measure its size accurately and to see the fœtal head in its relationship to the brim are a great advance on palpation alone The much quoted aphorism of Freeland Barbour The fœtal head is the best pelvimiter is still true as far as the brim is concerned but to know exactly the size of the whole pelvis brim cavity and outlet is invaluable because difficulty may arise below the level of the brim of the pelvis

Whether every pregnant woman should have her pelvis measured by X rays once is a debatable point but it would appear as worthy of doing as routine chest X rays which every pregnant woman is offered the chance of having performed If it were possible to have one lateral film taken which would show the two most important measurements—the antero posterior of inlet and outlet—it would be a wise investment Perhaps in the next few years it will be possible to record these measurements on miniature films and pick out the ones suspected of having contracted pelvis for full pelvimetry

I might add that in our cases only those women suspected of having a contracted pelvis on clinical examination have been sent for X ray pelvimetry The one exception to this is in malpresentation the commonest by far of which are breech presentations External cephalic version is usually attempted before pelvimetry is performed but if unsuccessful no breech cases should be allowed to go into labour without X ray pelvimetry having been undertaken The fœtal loss in breech delivery can be substantially lowered by making sure the pelvis is normal before embarking on vaginal delivery *I might suggest here that if one finds a breech presentation in a case of mildly contracted pelvis* one should always consider external cephalic version even under anæsthesia because otherwise a Cæsarean section at term will be necessary

Having diagnosed a contracted pelvis clinically measured it accurately by X ray pelvimetry and also shown the fœtus is normal what should be the modern line of treatment? Twelve years ago the problem was quite different Sepsis still took its toll in spite of the sulphonamides while none of the antibiotics were in common use Vaginal examination so necessary to judge the progress of a trial of labour accurately was strongly discouraged because of the risk of sepsis Cæsarean section was nearly always of classical type and if it could be done as an operation of election with intact membranes so much the better Anæsthesia in the labouring woman was not so well understood especially the fact that food tends to lie in the stomach for a long time Many babies and not a few mothers were lost because of inhalation of vomitus at operative delivery

In view of this one can undertand why it was customary to admit these patients to hospital and under anæsthesia if necessary attempt to fit the head into the brim of the pelvis If one succeeded labour was allowed to start spontaneously if not elective Cæsarean section was performed shortly before term Unfortunately *this method*

of treatment had its limitations, because if the lower segment was not properly taken up, it was impossible to make the head fit into the brim of the pelvis Also high inclination of the pelvic brim made this manœuvre difficult in many cases

Nowadays the position has changed and I would submit that any primigravida with a flat pelvis in whom the fœtus is presenting by the vertex, and in whom the obstetrical conjugate is over 3 5 in (8 75 cm) should be allowed to go into labour I would specifically exclude elderly primigravida, not only those of ripe age but those who have been married for many years without becoming pregnant All malpresentations especially breeches of course would be excluded Table V shows that there is over 75 per cent success in this group in obtaining vaginal delivery

TABLE V

Type of Delivery by Size of Pelvis
(Available Conjugate of Brim)

Primigravidæ Only

	Cæsarean Section	Forceps Delivery	Spontaneous Delivery	Breech Extraction	Craniotomy
4 in and over (outlet)	3 (1 elective)	7	3	1	
3 6 in 4 in	11 (5)	15	20		1
3 5 in and under	5 (2)	1	2		
Not recorded	2 (1)	3			
Total	21 (9)	6	25	1	1

What is to be gained by this line of treatment? Firstly one is certain that the patient is at term or as near term as she is likely to go It is often difficult to assess the size of a baby and by allowing labour to start naturally one is prevented from doing a Cæsarean section too soon and possibly delivery of a baby a month premature

Secondly it ensures that the patient is given a fair chance to deliver herself vaginally One is often surprised to find delivery in a primigravida extraordinarily easy where one anticipated difficulty in vaginal delivery if not failure Labour is not generally so violent that if vaginal delivery appears impossible a lower segment Cæsarean section cannot be performed with safety to mother and baby

Thirdly should Cæsarean section have to be performed for any associated cause in spite of contracted pelvis such as malpresentation prolapsed cord or inco ordinate uterine action vaginal delivery in a subsequent labour is much more probable if the cervix has been allowed some dilatation

The table also shows that in only 12 out of the 65 primigravidæ allowed any labour at all was Cæsarean section necessary As already mentioned some of the labours were extremely short in those having abdominal delivery and one can only assume that the patient went into labour before elective Cæsarean section could be carried out

As was stated already delivery must be undertaken in a properly equipped institution with medical aid available at a moment s notice If the patient has been assessed properly before term there is probably no need to admit her to hospital till labour starts The only slight risk is prolapse of the umbilical cord should the membranes rupture before she reaches hospital Very early rupture of the membranes before labour is properly established is not a good prognostic sign in a trial of labour because it often heralds a long labour with an inco ordinate uterus When the membranes rupture if the head is high it is a very wise precaution to examine the patient vaginally to exclude prolapse of the umbilical cord If found with an undilated cervix and a high head Cæsarean section is the only answer for the safe delivery of the baby

In a trial of labour a nurse should be with the patient the whole time not only to keep up her morale but to ascertain the length interval between and strength of the uterine contractions She should also keep a careful ear on the fœtal heart as after all this is our only method of judging how the fœtus is standing up to labour The patient should be encouraged to drink plenty of fluids containing glucose She should not be given much solid food as she has more than a 50 per cent chance of an instrumental delivery and nothing precipitates anæsthetic vomiting like a three course lunch

One should always remember that this is a trial of labour and to obtain a successful result the patient must have uterine contractions to dilate her cervix Over kindness in the early stages invalidates many a trial labour and one must beware of oversedation Pethidine is an invaluable drug when given at the right time namely when regular sustained contractions are occurring and the cervix is 2 3 fingers dilated Earlier than this one should be content with syrup of chloral Morphia is a valuable drug to give the labouring woman a restful sleep but must not be used within four hours of anticipated delivery

In assessing the progress of a trial of labour much can be learnt from abdominal examination the position degree of flexion and descent of the fœtal head One essential fact which cannot be found by this means however is the degree of cervical dilatation If labour appears to be progressing well with regular pains it is probably un necessary to assess the degree of cervical dilatation before the membranes rupture If the trial is progressing well the head may be in the pelvis and the cervix fully dilated when this occurs However it may be quite the reverse the head high and the cervix hardly dilated at all Vaginal examination is the only certain way to find out how dilated the cervix is with absolute accuracy Rectal examination has a small place when there is a normal pelvis with the head deeply engaged but in cases of contracted pelvis is not only indefinite but dangerously misleading One should never hesitate to examine vaginally on more than one occasion should there be doubt as to the progress of labour One can also feel

the degree of moulding and accurately diagnose the position of the fœtal head in the pelvis with relation to the degree of engagement, and also whether the vertex is anterior, transverse or posterior malpresentations such as face or brow can be excluded Good prog nostic signs when the membranes rupture are a head fitting well into the cervical ring, dilatation being at least four fingers and the leading part of the head approaching the ischial spines On the other hand a high head with the cervix hanging down like a curtain in front of it is of poor prognostic value

Just how long a trial of labour should be allowed to continue before active interference is undertaken depends on the progress made If the cervix is approaching full dilatation, and the head is engaged a vaginal delivery can be anticipated Sturrock (1938) has shown that after thirty hours of labour both the maternal and fœtal death rate rise whether disproportion is present or not I would therefore suggest that after twenty four hours in labour the position should be critically reviewed An abdominal examination should be made to assess the descent of the head and whether an occipito posterior position is possibly causing an inco ordinate type of labour Even if the membranes are intact a vaginal examination should be made to assess the dilatation of the cervix and the position of the vertex If there is a large caput or excessive moulding the head may appear to be lower in the pelvis than is actually true as regards the greatest diameter of the fœtal skull In such cases a single lateral X ray photograph may be of great value in showing the true state of affairs and prevent embarkation on a vaginal delivery which may be difficult or impossible

Should the examination show that cervical dilatation is nearly complete and the head descending one should let labour continue as a vaginal delivery possibly assisted should be obtained within a few hours On the other hand if the head is still high and free and the cervix only dilated a finger s breadth or two one should seriously consider terminating labour by Cæsarean section Inco ordinate uterine action of either the hypotonic or hypertonic type is supposed to be common in cases of contracted pelvis In my series of both abdominal and vaginal deliveries labour lasted over thirty hours in 16 cases that is roughly a quarter of all the primigravidæ who were allowed any labour This is more than twice the rate for primigravidæ taken as a group In 5 of the 16 cases Cæsarean section was performed mainly because of the failure of the cervix to dilate It has always been considered inadvisable to give uterine stimulants such as pitocin to women with contracted pelves because of the danger of ruptured uterus In the last few years a new drug has appeared in the treatment of inco ordinate uterine action namely dihydroergotamine In the patient with a normal pelvis it has been found to be an invaluable drug but we have not used it in cases of contracted pelvis complicated by disordered uterine action Gill and Farrar (1951) showed that the number of prolonged labours

could be substantially reduced by the use of this drug and consider that it acts by reducing the tone of the uterus If labour appears to be progressing well after twenty four hours even although dilatation is not far advanced one should let it continue for another twelve hours before reviewing the position again If progress has been maintained and delivery appears likely soon one should let well alone but if there is little or no progress Cæsarean section is strongly indicated One may criticise this labour by the clock but the fact remains that if an eye is not kept on the duration of labour it may drift on for days with the fœtus less able to withstand the ultimate Cæsarean section

What other factors might lead one to terminate the trial before vaginal delivery was possible? I have already mentioned the necessity of keeping a careful check on the fœtal heart Sometimes when the head is moulding through the pelvic brim marked slowing of the fœtal heart is noticed This should only be a temporary phase however and should the fœtal heart fail to return to normal one must consider abdominal delivery There has been a tendency in recent years to minimise the value of listening to the fœtal heart in labour and even at the British Congress of Obstetricians in 1949 Feeney stated that obstetricians should not be unduly fussed by the fœtal heart It should be stated however that he was soon challenged by Nixon because as is well known it is the only way one can assess how the fœtus is standing up to the trial of labour The fact remains that some fœtuses just will not stand the pressure and possibly anoxæmia of a trial labour and if not rescued in time will die even with intact membranes I notice that two of the Cæsarean sections in my series were performed for fœtal distress one at four fingers dilatation and the other at a tip with ruptured membranes while another was performed for prolapse of the umbilical cord I might mention here that fresh meconium in a vertex presentation is another ominous sign and should warn one to listen most carefully to the fœtal heart Sometimes when a Cæsarean section is performed for inertia or possibly gross disproportion early in labour one is surprised to find the amniotic sac full of thick meconium even although the fœtal heart is normal This is the type of case in which the fœtal heart stops suddenly and is most commonly found in elderly primigravidæ and cases of post maturity I would like to point out here that the only reliable signs of fœtal distress are variations in the rate of the fœtal heart usually marked slowing although occasionally a rate of over 160 per minute heralds severe fœtal distress I do not think the so called muffling of the fœtal heart is of any value at all because as the head descends the back rotates and changes in the audibility of the fœtal heart occur A fœtal heart rate persistently below 100 per minute calls for immediate delivery of the fœtus by forceps or Cæsarean section depending on the dilatation of the cervix and ease of delivery

Another factor that may occasionally force one s hand is maternal distress but if the patient has been adequately prepared for labour

by relaxation exercises and the position explained to her as regards vaginal delivery, these cases should be rare As a matter of fact it is the patient who has had an elective Cæsarean section for any cause in her first pregnancy who often takes labour very badly in the next one and demands a repeat section early in labour In both types an adequate sedative such as morphia usually relieves the pain temporarily but these patients are poor subjects for an extended trial of labour, as often as not they have disordered action of the uterus, possibly caused by the emotional upset A timely Cæsarean section in this type of woman may be justified as it also may be necessary in the woman who has been promised it elsewhere and nothing will convince her it is not necessary as an elective procedure

A third factor that may cause the trial of labour to be abandoned is the fact that the head is not able to descend into the pelvis I would like to emphasise here that while it is not necessary to let the cervix dilate fully before abandoning a trial of labour, it is necessary to let labour continue for some time with ruptured membranes Often on vaginally examining these patients one finds a large bag of membranes with the head perhaps a half inch behind Once the membranes rupture the head often fits snugly into the cervix and labour proceeds rapidly

What should be done when the cervix reaches full dilatation but the greatest diameter of the head remains high in the pelvis—just at the brim? This to my mind is the most difficult case to deal with of all because vaginal delivery is theoretically possible and having got this far one is reluctant to change one s tactics However the fact remains that a forceps at this level is dangerous to both mother and baby a lower segment Cæsarean section is to be preferred It is sometimes alleged that there will be difficulty in disempacting the fœtal head but in practice this is rarely found It is usually possible to lift the head out manually but some operators prefer one or both blades of the obstetric forceps Sometimes upward pressure on the anterior shoulder makes delivery easier The one stillbirth in a forceps delivery in a primigravida was in a case like this where the head was arrested high in the pelvis the actual cause of death being cerebral hæmorrhage

If the trial labour has been successful and I have shown that in over two thirds of the cases of contracted pelvis in primigravidæ this occurred one must be prepared to deliver by forceps in 50 per cent of the cases Therefore once the head is well into the pelvis and labour not progressing it is far better to examine the patient vaginally to find out if the delay is caused by malposition of the head either occipito posterior or transverse To wait for signs of fœtal or maternal distress is poor obstetrics and gravely prejudices the results It is of interest to note that in this series roughly half of the cases had a malposition in the occiput deep transverse arrest being that most commonly found As a control I keep a record of a similar number of primigravidæ

with normal pelves and found that while only 18 per cent. required instrumental delivery, lateral or posterior position of the vertex was even more commonly an indication for interference. One factor which plays a large part in safe delivery in this type of patient is adequate anæsthesia. If a fairly difficult manual rotation of the head is necessary good uterine relaxation is required. The only two drugs which make this possible are chloroform and ether, neither of which find much favour with the modern anæsthetist. In all types of transverse arrest Kielland's forceps have proved their value if manual rotation is impossible, but I do feel that it should be tried first.

A case of prolonged labour culminating in a fairly stiff mid cavity forceps is apt to show some degree of shock after delivery. I have found that an intravenous glucose drip for a few hours before delivery

TABLE VI

Type of Delivery by Weight of Baby
Primigravidæ Only

Weight of Babies	Cæsarean Section	Forceps Delivery	Spontaneous Delivery	Breech Extraction	Craniotomy
9 lb. and over	3 (1 elective)	1			
8-9 lb.	4 (2)	9			
7-8 lb.	6 (4)	9	10	1 } twins	1
6-7 lb.	7 ( )	6	9	1 }	
Under 6 lb.	1 (0)	[illegible]	7		
		(1 pr. twins)	(1 pr. twins)		
Total	21 (9)	[illegible]	6		1

is a very good prophylactic measure, and consider that a pint of fluid before delivery is of more value than a pint of blood after delivery. Also if there is any question of intravenous therapy it is a wise obstetrician who gets there first before the anæsthetist needs all the veins for his polypharmacy.

The main factor which appears to decide whether vaginal delivery will be spontaneous or not is the size of the fœtus. Table VI shows that if the fœtus is over 8 lb. (3.6 kg.) a forceps delivery is the rule. It also shows that the Cæsarean section babies were of all weights although there were a significant number over 9 lb. (4.1 kg.).

Turning now to the parous patient the treatment depends on two main factors in the previous history. There are firstly the number of living children and secondly whether a Cæsarean section has been performed or not. I might just repeat here that before embarking on the delivery of a parous patient with contracted pelvis one should assess the case as carefully as the primigravida with X-ray pelvimetry as well as clinical examination.

If one or more vaginal deliveries have resulted in fœtal loss the obstetrician is reluctant to try for another vaginal delivery lest the same result may occur. As I mentioned earlier the previous history

of many of these parous women is extremely bad and one may be compelled to offer the patient a Cæsarean section in the hope of obtaining a living child While elective Cæsarean section is not the perfect answer to the problem the fact does remain that it does give these women a better chance of a live child In the present series 2 babies to all appearances perfectly normal were lost at or after elective Cæsarean section This, out of 39 is probably higher than normal for the operation but nevertheless permits those who consider Cæsarean section the correct treatment for all cases of contracted pelvis to see its limitations

While vaginal delivery in cases of contracted pelvis with a Cæsarean scar is often possible and indeed occurred in 13 of my series I think we must be very cautious as to the advisability of allowing this to occur I have no hesitation in advocating vaginal delivery after a previous lower segment Cæsarean section where the pelvis is normal but consider when proved contraction is present this is subjecting the uterus to a big strain While it must be admitted there was only one case of rupture of a previous lower segment Cæsarean section scar in my series there were only 13 of these women who had any labour at all Another important point was shown in our January paper that the babies are nearly always heavier in a subsequent pregnancy whether vaginal or abdominal delivery is undertaken

If vaginal delivery possibly instrumental, in the previous pregnancies has resulted in living children we find that as a rule spontaneous delivery can be anticipated in the subsequent labours Possibly the most surprising feature of this whole paper was the low incidence of forceps delivery in the parous women One must however not be unduly complacent about vaginal delivery because as has been shown Cæsarean section was necessary in 10 women who had had vaginal delivery only previously One should never make sterilisation the excuse for doing an unnecessary Cæsarean section

Finally to sum up I do feel that if we are to reduce the number of unnecessary Cæsarean sections in contracted pelvis we must focus our attention on the primigravid patient Provided the pelvis is not grossly contracted these women should be allowed a good trial of labour as I have described not just a token one which is valueless We must however keep an open mind and if progress is poor or the fœtus not standing the trial well we must be prepared to step in and perform a lower segment Cæsarean section At the same time we must be careful that in our attempts to obtain vaginal delivery we do not lean over backwards and refuse to do a Cæsarean section when the need for it is obvious It is interesting to note that in the last three years a total of only 31 Cæsarean sections in primigravidæ were performed for contracted pelvis in the Simpson Maternity Pavilion considering that in 1947 no less than 46 were performed we are obviously heading in the right direction

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SOME PHENOMENA OF TONE IN THE GASTRO INTESTINAL TRACT

By JOHN B KING

THE choice of subject indicates no failure to appreciate the difficulties of discussing any aspect of tone whether in voluntary or plain muscle and I have indeed an acute awareness of the extent to which it is properly the province of the physiologist None the less there are many phenomena of normal and abnormal tonic states in the gastro intestinal tract which are constantly evident in routine clinical X ray work but which evade observation in the laboratory by clinical examination or at operation It is to some features of these conditions that I will confine myself

In the œsophagus the Plummer Vinson or Paterson Kelly syndrome and cardiospasm are both conditions which by their intermingling of functional element and organic change would suit this subject well, but so vast is their literature and so attractive are the conflicting theories associated with them that it may be better to consider an upset of tone which if rather rarer is not so involved in some of these difficulties The only case history given here will be that of a patient with a diffuse hypertonic state of the whole musculature of the œsophagus not because of the relative rarity of the condition but because it exemplifies so well features to be mentioned at other sites in the alimentary tract and because œsophagoscopy makes possible direct observation of the spastic state here in a way not possible elsewhere (Plate, Fig 1)

This man aged 64 had been admitted to the Royal Infirmary Edinburgh on four occasions in the previous five years, and was known to be suffering from cirrhosis of the liver bronchiectasis cardiac failure and marked vitamin A deficiency His dysphagia was only mild had been present for an indefinite period certainly for several years and there was no reason to relate it to his many established organic dis abilities While the difficulty in swallowing was noticeably intermittent the very abnormal state of the œsophagus was constant at all X ray examinations and had been the subject of interest during the previous periods of admission to hospital Œsophagoscopy done on more than one occasion confirmed the essentially spastic nature of the ring like contractions it was suggested that when pentothal was used the con strictions seemed to be deeper but to relax with less pressure than when no general anæsthetic was used No autopsy findings are available on this case but such examination in precisely similar cases have failed to reveal any organic changes whatever in the œsophagus and none of these cases which have been fully investigated appear to give ground

Read 3rd May 1951



Fig. 1.—Note deep peristaltic indentations involving the whole length of the oesophagus and forming the so-called tertiary contractions and pseudo diverticula

Fig. 2.—Note tonic adaptation to filling of the stomach. Figs. 1-5 Upright posture. Fig. 6 Prone. Note increased peristalsis





(a) (b)

FIG 3—Same patient upright posture Six weeks interval (a) Atony due to gastric ulcer of middle of lesser curvature No pyloric or duodenal obstruction (b) Recovery of postural tone following healing of gastric ulcer



Fig 4—Arrow at A indicates spastic segment of di tal colon which can remain filled with gas and shov no contraction while an enema fills th proximal colon

for believing that the condition in this patient was secondary to the vitamin A deficiency

Here then is a gross extensive and apparently functional condition of long standing of entirely unknown ætiology associated with no detectible post mortem changes By itself it is essentially symptomless only occasionally becoming evident to the patient by the difficulty in swallowing which it produces

The antithesis of this condition also occurs as idiopathic paralysis of the œsophagus in which the entire œsophageal wall appears healthy but flaccid does not contract on a bolus of food and shows no visible peristalsis on X ray examination while naturally the dysphagia is postural as gravity alone is available to pass the food into the stomach

Once established neither of those conditions seems to be progressive and the cases which have been followed up have died of apparently unrelated disease As neither the simple reporting of isolated cases with elaboration of nomenclature nor the formation of unsubstantiated theory are likely to advance the understanding of such conditions what is surely required here and in many similar gastro intestinal conditions is investigation by co operation with physiologist and pharmacologis

If only by the very difference of its motor function it is natural that the tone of the gastric musculature should be manifest in very different ways from that of the œsophagus Here more than at any other part of the gastro intestinal tract is seen postural visceral tone that form of adaptation of a hollow viscus to the form of its content never absent during life but ever varying in degree

Unfortunately the time has not yet passed when the small high stomach of the short broad individual is described as hypertonic and atonicity attributed to the normal state of the stomach in the long and lean Such stomachs are no more than normal variations of anatomical formation their shape is in no way related to any aspect of muscle tone and recognition of this is not without clinical application (Plate Fig)

Postural tone in the healthy stomach is most simply seen at X ray examination in the upright position as that state of contraction which keeps the opaque meal in the form of a column maintained against gravity and not as a simple level pool With recumbency the demand on the gastric musculature to maintain postural tone is removed or at least greatly diminished and this release of strain is immediately made evident by an increase of peristaltic contraction both in depth and frequency This close relationship between postural tone and the local intermittent tonic state of peristalsis is a normal phenomenon which be comes greatly exaggerated in the early stages of pyloric occlusion being indeed the earliest X ray evidence of this state These tonic changes are of more than academic interest thus vomiting is an exaggerated clinical manifestation of hyperperistalsis and its severity and speed of development can be very significant of the cause of the obstructing condition It is not really a common symptom of that stage of a duodenal

associated with gastric ulcer less well known but of great interest is that atony and dilatation which is present in some cases of peptic ulcer in the region of the incisura angularis The whole X ray appearance in the upright position is that of pyloric stenosis of long standing with complete or almost complete loss of peristalsis but examination in the prone position demonstrates that there is no antral pyloric or duodenal obstructing condition The mid lesser curvature gastric ulcer has in fact produced a failure of both postural tone and peristaltic activity the mechanism by which this effect is produced remains unknown (Plate Fig 3 *a* and *b*)

But all variations of tone are by no means of physical origin there is that sudden and sometimes complete loss of both postural tone and peristaltic contraction which follows fright A banged door, a dropped tray even an inept remark during fluoroscopic examination and it is common to see a stomach of normal tone allow its content to sag and take on all the appearances of organic dilatation Here in involuntary muscle is a manifestation of that feature of which Sherrington[2] wrote

Of all the reflexes it is the tonic reflexes *e g* of ordinary posture that are in my experience the most easily interrupted by other reflexes It is this loss of gastric tone unperceived by the individual just as much as the pyloric spasm of fear that is the cause of that gastric stasis of psychological origin which may persist to the extent of causing a twenty four hour retention of food

The problems of sphincteric tone involved in pyloric activity are of an excessive complexity In the first part of the duodenum there is that great tendency to local spastic contraction which makes possible a reasonable accuracy of X ray diagnosis in peptic ulcer and it is because spasm here may be so closely simulated by scarring that inaccuracy persists to a serious degree What seems to remain for investigation is the extent to which the extreme liability to local tonic contraction here is due to the same underlying physiological basis as is the tendency to ulcer formation

In great contrast is the distal small intestine in which the tone is such that an anatomical length of over twenty feet has to be equated with a physiological length of under seven feet yet this remarkable degree of constant contraction is consistent with an almost entire absence of any liability to local spastic phenomena It is true that ulcerating lesions are rare but they do occur and adhesions are common and when involving the colon it is there that spasm tends to take place But of the tonic phenomena here it is that involving the conception of reverse peristalsis which requires comment since there is wide spread acceptance of such action existing Certainly the rapidity of the progressive movements of the small intestine makes their study difficult but I know of no X ray evidence in favour of adoral peristalsis as a physiological action or under pathological conditions If a segment of bowel contracts symmetrically its content will tend to pass equally forwards or backwards and if a progressive movement takes place

ulcer when there is intermittent pyloric spasm, or of the early phase of a slowly developing fibrous stricture but is frequent in rapid occlusion whether by true tumour or inflammatory mass The next reaction of gastric tone to persisting or progressive pyloric obstruction is a diminution of both postural tone and peristaltic activity and as might be expected the rate at which the atonic state becomes evident is in direct proportion to the speed of the occlusion thus advanced gastric atony known to have developed over a short period is more suggestive of obstruction from tumour than from ulcer stenosis Much later in the formation of pyloric stenosis, when dilatation has developed and postural tone has ceased to be maintained no peristalsis is detectible with the patient upright, but deep contractions will still develop with recumbency, and be even more marked in the prone position than when supine The involuntary muscle of the stomach is here showing the state of which Sherrington[1] wrote "The waning of a reflex under long maintained excitation is one of the many phenomena that pass in physiology under the name of fatigue' ' These phenomena are also found in that relatively rare but interesting group of cases in which a true hypertrophic pyloric stenosis causes symptoms only late in life Here the gastric musculature has been equal to the strain of passing food through a narrow pylorus until with increasing years the power of tonic contraction becomes prematurely weakened similarly some of these cases only came to light under the undue fatigue of active service in war

Patients with great dilatation and atony from chronic stenosing duodenal ulcers are becoming rare formerly so common, their clinical history followed a most consistent pattern each stage corresponding to the tonic changes in the stomach The acute dyspepsia of the early active phase had often been almost forgotten while the memory of the vomiting of the later hypertonic state remained clear With the development of gastric atony vomiting ceased sometimes for years, only to recur in the terminal stages of advanced stenosis by which time the cachexia and anorexia so frequently simulated carcinoma Surgery perhaps more than medicine has found it necessary to consider and deal with some of the manifestations of tonic change as in acute post operative dilatation of the stomach or small intestine ileus but the more chronic changes are of no less importance In the era of gastro jejunostomy an anastomosis made at the optimum point in an atonic stomach not infrequently proved to be undesirably high following recovery of normal postural gastric tone and more recently the effects on gastric tone of simple vagotomy were of interest if only because of their long term unpredictability though the immediate tendency to post operative atony was indeed definite

Peptic ulcer of the lesser curvature is classically associated with a spastic indentation of the opposite greater curvature but why this spasm only occurs in certain cases is not known nor is there any evident relationship between the size of the ulcer in width or depth and the presence of the spasm Another form of tonic change in the stomach

A parallel but probably quite distinct group of cases are those in which sudden atony of an otherwise normal colon sufficiently marked to produce obstructive symptoms may be the first sign of advanced failure of renal function In the transverse and descending colon there is that normal formation known as haustration which is probably to some degree a manifestation of tone Attribution of haustration solely to the limiting effect of the tæniæ coli cannot be accepted for if the tæniæ are divided haustration to a large extent persists moreover in those pathological states in which the haustration disappears there is no reason to believe that there is any alteration in the length of the tæniæ There seems little doubt that the tæniæ act as fixed points for the contraction of the circular musculature and that the haustration is in part due to such a tonic state Research here would be of clinical value if it established the relationship between the extent of inflammatory involvement of bowel wall and that disappearance of haustration which is known to occur in ulcerating conditions

The spasm which so commonly occurs at the distal end of the descending colon is another and very different type of local tonic upset Just as pyloric spasm was for so many years a functional entity the existence of which was ignored or actually denied by many clinicians so the importance of persistent local spasm confined to an inch or two of distal colon and not related to any pathological condition has only slowly been appreciated While the state of general spasticity of the whole descending colon is readily accepted since it constitutes an entity which is clinically palpable the quite distinct state in which local spasm always occurs at the same point presents itself at X ray examination as an entirely different condition and of all gastro-intestinal tonic changes is apparently the one most frequently of psychological origin It is indeed strange that scepticism about this should be met even among those familiar with the capacity of fear to blanch the mucous membrane of the pelvic colon No explanation seems to be known of the actual mechanism by which it is constantly possible to fill the entire proximal colon and cæcum through such a spastic segment of bowel which relaxes to pass the enema but at no moment fills with the opaque medium (Plate Fig 4)

Sir John Fraser used to suggest an ecological outlook on these conditions of deficient nervous co ordination of the gastro-intestinal tract From the purely myenteric contraction of the sponge through the rudimentary nervous system of the sea anemone by a slow evolutionary elaboration of voluntary and involuntary nervous systems he saw the whole group of achalasias œsophageal pyloric ileal and rectal as failures in the formation of a harmonious autonomic system Less ambitiously it may be accepted that man in raising himself from his primitive pronograde posture has increased his liability to visceral tonic strain

Sir Heneage Ogilvie[3] has pointed out that astonishing extent to which an exaggerated disgust with all aspects of colon function is a

against a closed point there will be a backward surge of the content proportional in vigour to the strength of the forward moving contraction The presence of bile in the stomach or indeed of fæcal vomiting is not evidence of reverse peristalsis While the numerous references from the days of medicated enemata to complaints by the patients of the taste of the substance introduced are explicable by transpiration from the pulmonary circulation the repeated experimental finding in the mouth, of lycopodium spores introduced into the rectum twenty four hours previously, are admittedly more difficult to understand Recently there have been attempts to relate absorption abnormalities of the small intestine to changes in the mucous membrane form and thus to attach importance to the X ray appearances in these conditions and while certain deficiency states are no doubt associated with tonic changes in the small intestine, it is more than doubtful if any diagnostic X ray appearances have yet been established

One of the most interesting features of the ileo cæcal sphincter is that a structure so well defined anatomically gives so little evidence of function radiologically and there seems to be no evidence that it is capable of spastic contraction indeed the so called competence or incompetence of this valve is difficult of assessment as the maintenance of quite low pressure for a few minutes will allow an enema to enter the ileum in every case in which there is not organic obstruction and there seems to be no condition of ileal stasis unassociated with demonstrable obstructive lesions in the ileum, cæcum or colon Further evidence that the valvular effect by the ileo cæcal sphincter is indeed small is seen on X ray examination after the evacuation of a barium enema when the cæcal contraction will almost always be found to have passed some of its contents into the ileum and indeed this feature is or should be part of the routine procedure in the X ray examination of the ileo cæcal region

That dilatation of the cæcum which is such a constant finding in cases of distal colon spasm or indeed of any distal obstructive lesion is not indicative of atony but merely reflects the relative lack of musculature at this point It is becoming increasingly realised that at any one moment the amount of gas in the alimentary tracts is for all practical purposes the amount of air which has been recently swallowed and that the passage of ingested air from the stomach to the colon can take place in under fifteen minutes The actual distribution of the gas in the bowel depends on its degree of tonic contraction or dilatation, which is why gas not normally seen in the small intestine becomes of diagnostic value here in obstructive conditions A distinct entity is that gas distension of the colon seen in cases of renal colic which may be in part but is certainly not wholly due to excessive swallowing during the attacks of pain Distension of the renal pelvis would appear to cause intestinal relaxation hence the large proportion of cases in which there is a great increase in the amount of gas during the short period required to carry out retrograde pyelography

CANCER OF THE LARYNX

By Dr I SIMSON HALL and Dr J F O MITCHELL

CANCER of the larynx has been known since the earliest days of medicine but at first it was confused with other granulomatous conditions In fact even into the latter part of the last century it was held to be rare and it was not until Emmanuel Garcia in 1854 introduced the laryngoscope that it became possible to examine the vocal cords and the larynx itself so that differentiation between cancer of the larynx and other conditions became possible

Prior to the days in which inspection of the larynx was possible it was believed that cancer of the larynx was a disease occurring in the lower part of the pharynx and growing upwards It was thought then that extrinsic cancer of the larynx was the common disease The possibility of accurate examination of the larynx and the vocal cords altered the conception and intrinsic cancer soon became known as the commoner form of the disease This knowledge was not developed immediately and as late as 1894 Sir Felix Semon reported 55 cases of intrinsic disease but as these were all advanced it was impossible to determine the point of origin

It was only by the gradual accumulation of experience that we have come to realise the true distribution of cancer of the larynx

The early history of cancer of the larynx and its treatment is the story of the development of the operation of thyrotomy or laryngo fissure Alton Buck in America and Duncan Gibb in England in 1851 and 1864 respectively appear to have been the first to operate successfully upon intrinsic cancer of the larynx

All authorities of that day condemned thyrotomy or laryngofissure heartily and it was only in the closing years of the century that Sir Felix Semon and Butlin published figures showing that their operative treatments were meeting with greater success Even so the tale of unrelieved failures which is the story of the treatment of cancer of the larynx at that time cannot but evoke admiration for the frankness with which the cases are discussed and the disasters recorded

It is probable that the developments in surgery in general the development of anæsthesia and the pre operative preparation of patients were the factors which helped greatly to reduce the hazards of the operation

Read 13th November 1932

feature of primitive races, and may it be that the lack of scientific interest in the gross phenomena of intestinal function arises from a persistence of such atavistic inhibitions ?

Fischer[4] in suggesting that the difference in the physiology of striped and smooth muscle have been over elaborated, writes —

' Since the contractile mechanism in smooth muscle is so similar to that of striated muscle, where it can be studied under much more favourable conditions, the main task for the future concerning the physiology of vertebrate smooth muscles will be the analysis of the mechanisms by which contraction of the single muscle cells are integrated into the specific functions of the various smooth muscle organs '

Such a view may indeed be correct, but I have hoped to show that a vast field of readily accessible phenomena exist in the human subject the further investigation of which would advance physiological know ledge on lines of great clinical value

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3 OGILVIE H (1951) *Proc Roy Soc Med* 44 200-206
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carried out by different people that one realises how confused the situation is

The surgeon tends to classify the disease according to its operability in the sites in which experience has taught him the cancer is amenable to surgical treatment

The radiotherapist tends to classify the disease irrespective of its site into forms which are amenable to treatment by his particular method That is to say the stage at which the disease is found whether extensive or not extensive infiltrating or not infiltrating and its pathological characteristics are the points upon which his treatment very often is planned

Naturally to a surgeon the surgical classification is the one which appeals most and it is proposed to divide cancer into the time honoured groups of intrinsic and extrinsic Intrinsic cancer is that which is in some part of the larynx between the midline of the ventricular band and the sub glottic space Extrinsic cancer includes all those growths occurring above the mid point of the ventricular band and including the epiglottis and the outer surfaces or pharyngeal surfaces of the larynx

Symptoms

The symptoms of cancer of the larynx might have been thought to be so well known to everyone that early diagnosis of cancer would be the rule Specialist practitioner and student alike have all been impressed with the necessity that cases of unexplained hoarseness lasting more than six weeks should be examined by someone who has the necessary skill to see the vocal cords clearly But the fact remains that cases of cancer of the larynx which are advanced are frequently seen and which in many cases are past the stage of operability when seen

The fear of what is likely to be found prevents some people coming for early advice but these must be comparatively few Therefore the conclusion which can be drawn is that the symptoms of cancer instead of being early and obvious are later and equivocal

Should the cancer occur on the vocal cord itself then interference with phonation is caused with the probable result that early diagnosis is as ured In some cases however this type of disease is not seen in the earliest stages for the reason that there is some other condition present which masks the early cancer so that the patient is under the impression that the symptoms of malignant disease are merely an exaggeration of the normal Such conditions as chronic catarrh or a smoker s cough are common examples

In other cases where the cancer takes origin in the subglottic space in the anterior commissure or in the vestibule nothing but an occasional clouding of the voice may be noticed or clearing of the throat and even the cancer may on occasions be found to have caused symptoms which can disappear for weeks or even months and then reappear as the growth spreads and involves the moving parts of the larynx

In Britain in the early years of this century the operation of thyrotomy or laryngofissure was accepted quite readily In America it was more slowly accepted, while in Scandinavia it made little or no progress The reason for this is fairly plain There is no doubt that Sir St Clair Thomson, who in the days before the war was accepted as the doyen of laryngology in this country by his outstanding skill and personality raised the treatment of cancer to a new level of success and ensured acceptance of his ideas Sir St Clair Thomson and his associate and colleague Mr Lionel Colledge were the pioneers of modern laryngeal surgery in this country

Radiation treatment of cancer of the larynx did not show any progress until Coutard in 1921 developed the method of fractionated treatment which is essentially the modern treatment of cancer by X rays

Shortly afterwards Ledoux and following him Harmer developed the technique of fenestration of the thyroid cartilage in which by window resection radium needles were inserted close to the laryngeal mucous membrane and thus radiation of the tumour was obtained

Radiation treatment at first had a poor record comparatively for surgery had a long start and its success was already established but recently radiation treatment of cancer has made such progress that it is now being maintained in many quarters that treatment by radiation is superior to treatment by surgery One thing which must be remembered is that radiation while not in its infancy, is still in a state of development

This has been taken to mean by some that surgery has run its *course and is now outmoded but it seems that any prophecy along* these lines is foolish for only a few years ago it would not have been thought that the introduction of antibiotics would have rendered the after treatment of laryngectomy comparatively simple and robbed that operation of virtually all its dangers

Who can say what the future will hold or in what way laryngeal surgery can make use of general advances in medicine and therapeutics ?

INCIDENCE

The incidence of cancer of the larynx as a disease is not the subject of the discussion at the moment but it cannot be said to be a common disease The fact that leading authorities in this and other countries can muster only a very few hundred cases shows that it cannot be classed among the common diseases It is predominantly a disease of males

CLASSIFICATION

It might have been thought that a classification of a disease such as this is *comparatively simple* It is only however when one attempts to make comparisons between the results of various forms of treatment

PATHOLOGY

The nature of the tumour has been determined in every case in this series A very few cases had unusual forms of growth which have been excluded from this study and therefore in all those cases which are described in detail squamous epithelioma was confirmed

Considerable use has been made of pathological classification as an indication for treatment by one method or the other Broder s classification was considered to be of considerable importance but apart from a broad indication it is not relied upon to determine treatment It has been found difficult to distinguish between Broder s classification Nos 2 and 3 for it has become evident that tissue taken from different portions of a tumour may show different histological characteristics

It has been the custom therefore to divide the tumours into three groups the highly differentiated the moderately differentiated and the undifferentiated Further it has been shown by more than one worker that differentiation and curability are not antagonistic While it is possible therapeutically to eliminate a Broder s class 4 type of tumour with rapidity, experience has shown that permanent cure either by surgery or by radiation is extremely unlikely and the results in these classes of tumour have been poor

The meaning, therefore, of pathology from the point of view of treatment is that in the highly differentiated tumours and those that are not undifferentiated the possibility of cure is very much greater than in the less differentiated whether surgery or radiation is decided upon There is one qualification to this in that where metastases are shown to be of highly differentiated type surgery rather than radiation is indicated

TREATMENT

In intrinsic cancer we have available surgery or radiation in its various forms Surgery may consist of laryngofissure or of laryn gectomy In radiation there is available radiotherapy teleradium or the local insertion of radium by the Finzi Harmer technique

The laryngofissure operation is in most cases a simple procedure its mortality is practically nil and the interference with function is comparatively small The operation consists of splitting the larynx in the midline and thereafter the resection of the affected vocal cord and its underlying cartilage and obviously such treatment is only available for those cases in which it is possible to resect the tumour completely with a safe area of normal tissue surrounding it It can be applied however not only to those cases of limited cancer in the middle of the vocal cord but it can be used in those cases in which the cancer has crossed the midline by what is known as the midline technique suggested by Jackson in which the cartilage only is split in the first instance and the soft tissues containing the tumour are

Where attention has been drawn to the larynx and when cancer exists in or around the larynx the diagnosis is comparatively easy to those with the necessary skill The important point is that the person making the diagnosis should realise the responsibility of a negative finding That is to say, while it is perfectly simple for the comparatively inexperienced to diagnose a cancer which is well established it is after all in the earliest stages that it is necessary to make our diagnosis because in the earliest stages there is the best chance of making a cure Should therefore such a growth be present *it is possible that those unaccustomed to examining the larynx* constantly may miss the earliest stage of the disease and deprive the patient of his best chance of survival

Therefore if the person examining the patient is not completely certain that every portion of the larynx has been seen clearly and in a good light that patient should not be dismissed with a negative diagnosis *And further, where a clear conclusion has not been reached* the patient should be warned that further examination will be required within a very few weeks No patient should be dismissed without the instruction that should the symptoms continue for another three or four weeks further examination must be carried out

The appearances of the established carcinoma of the larynx are well known The slightly reddened rough excrescence typically at the junction of the anterior and middle thirds of the vocal cord are familiar, but it is where the appearances are not typical that the difficulties in diagnosis may arise

Where any deviation from the normal in the appearance of the vocal cords or any part of the larynx exists the routine which is general in all abnormalities of the mucous membrane of the upper respiratory passages must be followed in that the blood Wassermann reaction X ray of the chest and a biopsy are carried out From the information yielded by these examinations a diagnosis can be made in most instances

It is possible however that even after these precautions have been taken the diagnosis may not be certain Occasionally where epithelial overgrowth occurs such as in a pachydermia of the larynx or the condition known as keratosis the appearances may be uncertain *Continued observation is required in these cases* because further examination may show the breaking down of the tissue and the aberrent growth typical of carcinoma

From observation of many of these cases over prolonged periods it is recommended that a limited keratosis of the larynx should be removed endoscopically if sufficiently small If too large for this condition then laryngofissure or thyrotomy is justified If the condition spreads and becomes *generalised in the larynx the probability is that* that condition will become malignant and if it does so there is no alternative to laryngectomy

anterior commissure mobility also should be unimpaired This type of case is called the limited chordal cancer

Where there is anterior commissure involvement subglottic involvement or vocal process involvement the prospect of surgical success is considerably modified

All cases reported must satisfy the five year criterion in that they are alive and free of cancer for five years following operation

TABLE I

Total number of cases seen			175
Total number of cases intrinsic		81	
Total number of cases extrinsic		94	
Treated by surgery	32		
Treated by radiation therapy	103		
Treated by surgery and radiation (fenestration)	12		
Unfit for any treatment or given palliative treatment only	8		
	175		

One of the chief criticisms against surgical reports is that they are of selected groups of cases that only the less likely cases for treatment are handed over to radiotherapy and that therefore all cases are not included and a true picture is not obtained

TABLE II

Period 1933 1942

Number of cases		40
Intrinsic	12	
Extrinsic	8	
5 year survival	4 (10 per cent)	
Radium implantation	7	
5 year survival	2 (28 per cent)	
Total number for this period		47
General survival rate		13 per cent

It is possible here to make a fair comparison between surgery and radiation for between the years 1933 and 1942 no surgery whatever was carried out upon the larynx for the cure of cancer All cases in this period were handed over for radiation treatment The only operations performed were done for the insertion of radium needles by Finzi Harmer technique This occurred on seven occasions during this period

During this period the five year survival rate for radiotherapy in all cases is 10 per cent and one must admit at once that this is probably not a fair estimate because 7 cases probably very well suited to radiation were extracted for the purpose of Finzi Harmer treatment If however these are included with the radiation cases which they should be the percentage of five year survival is 13 per cent (Table II)

resected in one block with a sufficient margin of healthy tissue which includes the anterior part of the other vocal cord

RADIUM FENESTRATION OPERATION

This operation, known as the Finzi Harmer operation, consists of the insertion of a palisade of radium needles against the cancer bearing portion of the mucous membrane of the larynx They are inserted through a window cut in the thyroid cartilage The disadvantage of this form of treatment is that dosage of radiation is extremely difficult to calculate with any accuracy Secondly the dose is fixed and once the radium needles are inserted there is no possibility of modifying the treatment On the other hand there is no doubt that the functional result is excellent and the general disturbance of the patient is probably less than with any other form of treatment Treatment in the hands of some by this method has been good

TREATMENT OF EXTRINSIC CANCER

Extrinsic cancer of the larynx may be treated either by surgery or radiation Surgically speaking laryngectomy is the only operation which is of value except in certain very localised conditions for instance where cancer has attacked the epiglottis, epiglottidectomy may be successful in curing the disease On the other hand where the cancer has progressed beyond the larynx, laryngo pharyngectomy sometimes offers a chance of survival but the survival rate of this particular form of treatment is so low that it is probable that radiation will do as much if not more than surgery and with a great deal less suffering to the patient

Where the cancer has progressed beyond the larynx to the gland drainage areas and produced metastatic deposits the condition may be treated either by surgery or with radiation In the past reliance has been placed chiefly upon radiation in this particular condition but a study of the results of others has induced the opinion that surgery by block dissection is the correct method of treatment and will give better results where a possibility of cure exists than radiation

RESULTS OF TREATMENT

A series of 175 cases of squamous epithelioma of the larynx which have been seen in the Unit under one author s charge in the Royal Infirmary Edinburgh have been analysed In this series intrinsic and extrinsic cancer are fairly evenly divided and a general classification of these cases is given (Table I)

In considering results in intrinsic cancer it is first necessary to give a further classification of intrinsic cancer from the point of view of surgery The ideal case for surgical treatment is that in which the cancer is limited to the free edge of the vocal cord itself in which it does not touch the vocal process and does not extend into the

Fenestration of the Larynx

The operation of fenestration of the laryngeal cartilage by the Finz Harmer technique has been carried out on twelve occasions The results are shown in Table VI Although at first sight the figures are not impressive it is noteworthy that while the first 7 cases of the

TABLE VI

Finzi Harmer Operations

Total cases 12 Five year survival 7 = 58 3 per cent

12 were comparatively unsatisfactory the last 5 cases represent very much improved results The last 5 cases in fact have all survived the critical five year period It is probable with such a small number that coincidence has played a large part in the production of this result but the surgeon naturally can be excused for wishing to think that increased ability in the selection of cases and increase in skill in the performance of the operation have had some part in the production of this recovery rate of 100 per cent

The results recorded by others are shown as a comparative table compiled from some of the most recent and up to-date results in limited chordal cancer of the larynx as recorded in the literature There is no doubt that one of the outstanding surgical series has been produced by Gordon New and his co workers in the Mayo Clinic when they can record over 93 per cent of success in a series of cases of cancer of the vocal cord Admittedly this series is a highly selected one they are cases which must be considered as absolutely ideal for the treatment of cancer but that any recognised form of cancer can be considered as over 90 per cent curable is in itself a remarkable achievement It is only very recently that radiation has produced results approaching this (Table VII)

TABLE VII

Surgery			*Radiation*		
Hayes Martin	–	95 per cent	Baclesse	1951	90 per cent
New	1947	91 7	Neilson	1951	89
Tucker	1948	86	Harris	1951	87
Jackson	1948	81	Lenz	1947	80
Colledge	1945	85	Lederman	1952	83

Up till the last eighteen months results of radiation treatment fell considerably below the published figures of surgery particularly in this country but attention is drawn to the figures produced by Lederman of the National Throat Nose and Ear Hospital and the Royal Cancer Hospital who using teleradium has given a most encouraging report of this particular form of treatment Although his results do not yet equal the best figures obtained by surgery at least they seem to be a considerable advance upon anything else so far published here

Within the next five years up to 1947 surgery was again brought into use, and over this period including those cases which were submitted to radiation treatment with the intention of obtaining cure the survival rate was 35 1 per cent Again it must be emphasised that at this period radiation was far from the developed science which it is to day, while surgery was probably in a more advanced condition and therefore the picture is biased towards surgery and comparison is unfair

A detailed analysis of the results of laryngofissure is shown in Tables III and IV Experience is limited to 25 cases of laryngo

TABLE III

Laryngofissure operations		24
Over 5 years	Alive and well	Percentage
15	12	75

fissure and the general survival rate is 75 per cent the number available for five year analysis is 15 For limited chordal cancer nine out of ten survive the five year test

TABLE IV

Distribution of Growth

Site		5 year survival
Limited chordal	10	9
Anterior commisure	3	2
Vocal process	1	1
Anterior commisure and vocal process	1	0

The results of radiation treatment in cases of intrinsic cancer of the larynx are given in Table V A total of 42 cases was submitted

TABLE V

Radiation Treatment

Intrinsic cancer		42
Radiotherapy	24	
Finzi Harmer	12	
Mass Unit	6	
Five year survival	34 2 per cent	
Limited chordal cancer		12
Five year survival	66 per cent	

to radiation and the survival rate is 34 2 per cent In considering these results it is important to remember that the alternative surgical treatment in many instances was laryngectomy These results therefore cannot be considered in a comparative sense with those shown in Tables III and IV which were selected as suitable for conservative surgery Amongst these cases however is a group of 12 which come under the heading of limited chordal cancer and amongst these the five year survival rate is 66 per cent

Only a short time before the war one of the leading Continental authorities declared that he now did not attempt to obtain primary closure of the pharynx The introduction of antibiotics has revolutionised treatment in this operation for now it is expected in the vast majority of cases that primary healing is obtained and that there is no leakage and no fistula formation in the neck

There is a variety of methods by which the operation is carried out A straight midline incision is used for the technique known as the narrow field operation There are also the wide H shaped incision and the long U flap of Sorensen Each has its use but the midline or narrow field technique is steadily gaining popularity from the laryngologist s point of view

The wide technique which is sometimes used in America on the Continent and in this country has the advantage that should complete dissection of the glands of the neck be desired at the same time it permits of such wide excision Whether this treatment can be judged appropriate where there are already metastatic deposits present in the glands of the neck is open to question Some prefer to rely upon radiotherapy because the results of laryngectomy and gland excision where metastatic deposits have already occurred are extremely poor and the patient s chances of survival are very slender by any method of treatment

The U incision was designed to give added support to the weakness which was inevitably caused by the removal of the pre tracheal muscles and it has been criticised as being the least well supplied flap as regards blood and therefore more liable to necrosis than any other It has been said that where previous radiation has taken place it ought not to be employed Curiously enough it is just in that particular situation the writer has found it of the greatest use In laryngectomy after radiation it is difficult sometimes to be perfectly certain just how wide the excision of pharyngeal wall must be even of part of the œsophagus and this particular form of incision allows the greatest latitude and covers the largest number of possibilities where the excision may have to be extended By a modification of the usual technique trouble from lack of viability in this flap has been avoided The flap is raised completely ten days or so prior to the laryngectomy and then stitched back into place so that when the main operation is carried out the flap has already established its collateral blood supply and there is no difficulty arising from the interruption of the normal flow It has the further advantage that where there is marked fibrosis in the tissues of the neck following radiation it can be dealt with in a wide field In addition there is nothing to prevent the narrow field technique being undertaken after the flap is raised and in some ways the advantages of both a wide exposure and a narrow field technique are obtained

The midline method was suggested first of all by Crowe and in it the pre tracheal muscles are removed only in part The sternohyoid

It is the custom in many articles, particularly on the results of radiotherapy, to declare that while the results of surgery are good as good results or better can be obtained by radiotherapy while the *function obtained after radiotherapy is very much better than that* after surgery This seems to be an overstatement for results of treatment must be judged by those which are obtained on the average, and while radiation therapy results are outstanding in a few instances they have not yet reached the generally high percentage of success which is obtained by surgical means The necessity of the preservation of *function has been exaggerated, for a slight superiority in function is* a high price to pay for say a 10 per cent smaller chance of survival

Although it may be said that subsequent laryngectomy always gives a second chance the surgeon has one good chance only of curing cancer and that is in his first selection of a suitable form of treatment Should the question of function be that of absolute economic importance then the issue *must be put plainly to the patient* and his must be the decision to forego the best form of treatment in favour of another which will give him the greater chance of continuing to earn a living

Extrinsic Cancer of the Larynx

Seventy eight cases of extrinsic disease have come under my observation Treatment in this group consisted of X ray therapy or palliative surgery with the possible exception of one case of epithelioma of the epiglottis in which radical excision was possible

Laryngectomy was undertaken in one or two cases of subglottic extension after radiotherapy but without great hopes of cure

The results of treatment in this group of cases are uniformly depressing Only 54 cases were considered likely to benefit from *treatment and of these two have survived five years*

Of those treated with palliative surgery none survived one year

In spite of this there is no doubt that in the majority of cases treatment gave a valuable prolongation of life and reduced suffering This renders it well worth while continuing this form of treatment

Laryngectomy

Laryngectomy is practically speaking the only surgical operation which is available in the majority of cases for extrinsic cancer It must be fairly obvious therefore that it must take second place in general to radiotherapy The operation of laryngectomy was first carried out *in Edinburgh by Patrick Heron Watson but the credit is* somewhat lessened when one learns that the operation was proved *to have been carried out for syphilis rather than for cancer*

The operative mortality for laryngectomy for many years was high, owing to the incidence of sepsis and lung complications One of the chief disadvantages was the breaking down of the pharyngeal wound and the formation of a pharyngostome

speech and for those there are other methods such as the use of an artificial larynx which at least enables them to form words and make themselves understood

There is no doubt that loss of one of the most important functions is a serious blow to a patient but these advances do a great deal to render the loss tolerable

The survival rates of extrinsic cancer make sorry reading and the chief hope of improvement is in finding these cases at an earlier stage How far that is possible is not clear for the earliest signs of cancer of the external portions of the larynx are so masked and so equivocal that it is comparatively rarely a diagnosis is made in time for curative treatment All that can be done at present is to study and improve the methods of treatment but it is probable that in radiotherapy the greatest advances in treatment of extrinsic cancer will be made

The writers wish to point out that in many instances in the work described their part has been that of diagnosis only and the credit for the success of treatment is due to the care and skill of the staff of the Radiotherapeutic Department in the Edinburgh Royal Infirmary under the charge of Professor Robert McWhirter To the devotion and skill of the Nursing Staff of the Otolaryngological Department many of the patients owe their lives and the surgeon s burdens have been immeasurably lightened by their constant help and co-operation All the operations referred to have been carried out by the writers with the exception of one by the late Dr G Ewart Martin and three by Dr A Brownlie Smith

muscles are used in a muscle overlap in order to strengthen the midline and in stitching the second layer of sutures of the pharyngeal wall a bite of muscle is included in each suture with the result that the pharyngeal opening is welded closely to the muscular sheath and the other muscle is overlapped on the top giving a solidity and a support which in the majority of cases secures primary union

A further advantage in carrying out this technique is that the mid portion of the hyoid bone can be resected in the course of the operation Although this is not strictly necessary it has the added advantage of enabling wide retraction of the sterno hyoid muscle and also gives added facility and access in the accurate stitching of the pharyngeal wall

In all cases therefore where the cancer has extended beyond the limits which have been defined for the laryngofissure operation, this operation is the method of treatment chiefly employed where surgery is decided upon

As far as the majority of these cases of extrinsic cancer are con cerned radiotherapy should in the main be the first choice This does not mean that radiotherapy is to be given the chance of salvage treatment only but since it depends not so much upon the location of the growth as upon its state of development, radiotherapy will stand as good a chance or better of giving good results without the mutilating operation which surgery would involve This is an aspect of the subject in which further information is required and it is difficult for one surgeon to see sufficient cases on which to form a hard opinion Impressions may be erroneous and further evidence is needed from the work of many to enable accurate conclusions to be drawn

The after treatment of these cases does not require much comment Feeding by nasal tube is required for approximately twelve to fourteen days The ninth and the tenth are the crucial days in which fistulæ will make their appearance if they are going to form

No account of the operation of laryngectomy would be complete without some reference to the loss of the chief function of the larynx, for the deprivation of voice may cause profound psychological disturb ance in some patients and they have to be prepared for it with care

There is no doubt that the development of œsophageal speech has done a great deal to relieve the operation of some of its terrors for the patient and such use can be made of this that patients can continue to earn a living in occupations which demand talking as part of the job Intelligence and determination are of prime importance and we have found that example is one of the most effective method of teaching For a patient waiting to have such an operation to be visited by another patient who has been through it and to find that they can be cheerful and can carry on a conversation is most heartening and a sure method of bringing the patient to the operating theatre in the proper frame of mind

Not all patients however succeed in learning to use œsophageal

in this country in the early 1920 s although there was a long delay before the lessons learned there were applied to hot climates

Attempts to obtain assistance in the understanding of the effects of environmental heat from the medical literature are handicapped by an inadequate terminology in which some of the names used appear to be freely interchangeable among different syndromes This lack of a standard terminology is probably one of the factors which have perpetuated confusion Since the various physical components of the environment can be accurately measured and a great deal is known about the physiological responses of the body to heat it ought to be possible to deduce what the effects will be when physiological limits are overstepped In no group of diseases should applied physiology be of greater value in forecasting and interpreting pathology and in treatment

My object is to show that there is a close relationship between climatology applied physiology and pathology and on this basis to present a classification and terminology of the various heat effects syndromes These are not necessarily definitive since there are still gaps in our knowledge of the subject but it is hoped that they will help to clarify the present confusing situation It will be possible to refer here only very briefly to the clinical features of the different syndromes and only indirectly to their treatment More profitable will be emphasis on the physical physiological and climatic principles involved

Physical Aspects of Heat Regulation of the Body

The human body is homoiothermic but it is capable of functioning over a considerable range of temperature although brain cells cannot survive long when the blood temperature is much above 106 F (41 C) The optimum temperature of approximately 98 F (36 8 C) is maintained by a balance being struck between heat gain and heat loss

Heat production in the body is the result of chemical reactions and it is considerably increased by physical exertion and in fever When the environment is hotter than the body heat is transferred to the latter by the physical processes of radiation and convection The degree of effort required to dissipate the combined metabolic and exogenous heat (*heat gain*) in order to maintain thermal equilibrium is known as *heat stress* (heat strain heat load) *Heat loss* from the body can take place by means of radiation convection and evaporation conduction plays almost no part except in the transfer between the deeper tissues and the skin The rate of exchange of heat by radiation and convection depends on the difference in temperature between the body and its environment being less as the two are approximated Heat transfer is of course modified by clothing

For all practical purposes the skin radiates as a perfect black body

THE EFFECTS OF ENVIRONMENTAL HEAT

By G O HORNE, Ph D F R C P E
From the General Infirmary Leeds

INTRODUCTION

THERE is a great deal of misunderstanding about the effects of environmental heat on the human body and ignorance and confusion have undoubtedly contributed to the large number of heat casualties that have occurred especially during the two world wars It is still sometimes necessary for people to be exposed to the hazards of environmental heat and casualties are known to be still occurring and sometimes unnecessarily It must be admitted, of course that even when all the problems concerned are thoroughly understood heat casualties may not always be preventable especially under active military service conditions when the ' exigencies of the situation may be outwith the control of medical science Nevertheless the occurrence of some syndromes is now as inexcusable as is the mismanagement of any of them when they do occur

Only when military personnel are on active service can large numbers of heat effects syndromes be studied in the field, and the circumstances in which they occur are rarely favourable for research Little interest was shown between the wars on the effects of heat and experimental investigations were undertaken too late in the second war to reap much reward A certain amount of enthusiasm for the subject has persisted since the end of the last war and important contributions have recently been made by various investigation units sponsored by the Medical Research Council and the Royal Navy and by physiological teams in America

Heat effects syndromes are usually associated in the mind with the hot climates of the tropics and subtropics and with heatwaves in temperate climates but they are also encountered in other naturally occurring hot environments such as deep mines and in artificially produced hot environments such as steel mills and boiler rooms Indeed some of the pioneer work on the effects of heat was done in deep mines

Read 29th October 1953

The principal factor influencing heat exchange by *radiation* is the temperature of the surrounding objects relative to the skin but the humidity of the air interferes with the transfer of radiant energy Radiation occurs from approximately 85 per cent of the surface of the body and so posture may be an important factor in heat regulation when radiation temperatures are high Heat transfer by *convection* varies with the temperature of the air but does not vary much with its humidity it is considerably enhanced by air movement up to a velocity of about 70 miles per hour

If the environment is cooler than the body metabolic heat can be dissipated by radiation and convection but at higher temperatures *evaporation* is essential if thermal equilibrium is to be maintained The loss of heat by evaporation from the lungs is relatively so small as to be unimportant A small amount of heat is continuously being lost from the skin as a result of evaporation of insensible perspiration (the fluid that reaches the surface by diffusion through the epidermis) but when the air temperature reaches about 84° F (29° C) the lightly clothed body even at rest requires the secretion and evaporation of sweat in order to maintain thermal equilibrium

The greater the heat stress the more sweat for evaporation is required but sweat that drops off the skin gives no contribution to heat loss The rate of evaporation of water varies inversely with the relative humidity of the air and can be greatly augmented by increasing air movement Sweating also has the effect of allowing more heat to be lost to the air without increase of surface temperature since the relative humidity of the skin varies closely with its thermal conductivity Sweat contains approximately 0 2 to 0 3 per cent of salt

The *regulation of heat balance* is probably controlled mainly by centres in the hypothalmus which operate through the autonomic system The principal mechanical factors concerned are the distribution of the blood the circulation rate and the blood volume and when these are inadequate for heat loss sweating These factors are discussed later

The dry bulb temperature by itself is an inadequate expression of heat stress imposed by the environment in view of the importance in body temperature regulation of the humidity of the air and air movement More informative is the *effective temperature* which takes into account both of these other factors An even more accurate index is the *corrected effective temperature* which also considers the radiation temperature The estimation and calculation of these expressions is relatively simple (Fig 1)

Physiological Adaptation to Heat

The body has a remarkable power of adapting itself to heat and thus allowing existence and even healthy activity in hot environments Many factors are concerned in this process of adaptation

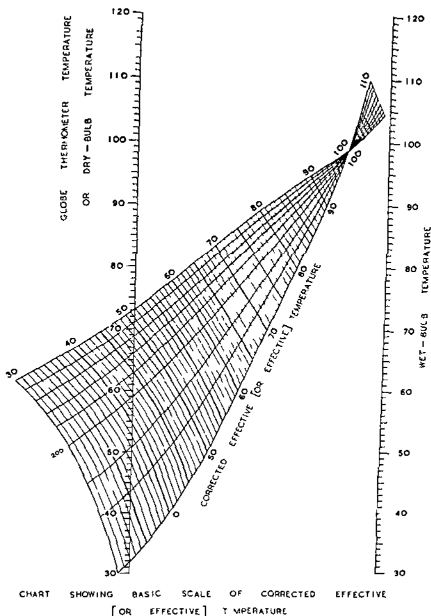


FIG I —Chart showing normal scale of corrected effective (or effective) temperatures (for persons wearing normal clothing)

The right hand vertical scale represents the wet bulb temperature The left hand scale represents the globe thermometer temperature or the air temperature according to whether one is determining the corrected effective temperature or the effe tive temperature

The sloping grid consists of a series of curves each of which is a scale of corrected effective (or effective) temperature corresponding to the air velocity shown at the lower end of the curve I ines are drawn through points on the different curves representing identical corrected effective (or effective) temperatures so that values for intermediate air velocities can be accurately read —(From *Environmental Warmth and its Measurement* Bedford 1946 By permission of H M S O)

of these temperatures but they do not necessarily maintain them at a normal level even when the body is functioning adequately There appears to be an alteration in the thermostat setting and work may be done better when the rectal temperature is slightly raised Only when the temperature is considerably raised do symptoms become prominent and danger imminent The upper limit of sustained rectal temperature compatible with survival is probably about 106° F (41° C)

Respiration—Pulmonary ventilation plays a relatively small part in the maintenance of thermal equilibrium though it is definitely increased when the body temperature is raised This hyperpnœa may cause alkalosis

Basal Metabolism—There is no conclusive evidence that basal metabolism is greatly altered in the process of adaptation to heat

Tolerance to Heat

Dramatic experiments in the past have illustrated the amazing capacity of the body to withstand great extremes of heat for short periods of time but these are of little other than historic importance since they are very rarely necessary Nowhere on earth does the daily maximum shade temperature average more than 120° F (48 8 C) in the hottest month of the year Conditions worse than this however may occur in artificially hot environments such as the stokeholds of ships and in deep mines

The *limit of human tolerance to heat* in terms of environmental temperature levels and time can be calculated on the theoretical consideration of hea exchange between the body and its environment Attempts have also been made to determine experimentally limiting environmental conditions for example for men uniformly dressed and working at different rates Other attempts have been made to define the limit of tolerance by studying the occurrence of heat casualties in relation to climatic conditions Many of these studies have a limited application in the field however because of important factors which are sometimes neglected in the calculations Men sometimes work without casualties in environments which are beyond the theoretical and experimental limits of tolerance and *vice versa* heat casualties sometimes occur well within these limits There seems to be little doubt however that in practice the wet bulb temperature is the limiting factor which determines the ability of man to maintain thermal balance in hot surroundings air movement is also very important In other words one of the most important limiting factors in the environment is the rate at which sweat can evaporate

Whilst it is therefore difficult to define the limits of tolerance to heat in terms of environmental conditions it is known that individual tolerance to any particular environment can be considerably increased This phenomenon is known as *acclimatisation to heat*

Circulation—Whilst a certain amount of heat can be transferred from the deeper tissues of the body to the surface by conduction the main burden is borne by the circulatory system and its adjustment for the task is essential if thermal equilibrium is to be maintained It acts by increasing the blood flow through many parts of the body, including the skin and voluntary muscles (to assist with conduction convection and radiation and to provide fluid for the sweat glands), the lungs (to provide adequate respiratory exchange) and the alimentary tract (to assist in the transfer of fluid to the surface) The adjustment is made by an increase in the minute volume of the heart (similar to the increase produced in response to physical exertion), by alterations in the vasomotor mechanisms, and by an increase in the blood volume Physical work puts an additional stress on the circulation and even maintenance of the erect posture will increase the stress because of the gravitational pooling of blood in the lower part of the body On exposure to heat there must be a continual struggle between cutaneous vasodilatation in order to lose heat and vasoconstriction to avoid pooling

Water and Salt Balance—The water output of the body in a hot environment depends principally on the amount of sweating required to maintain thermal equilibrium There is considerable individual variation in sweating function but the rate of sweating depends mainly on skin temperature and extremely high rates (up to 3 or 4 litres per hour) can be achieved for short periods The sweating mechanism appears to be fatiguable when extremely high rates are called for more so in humid than in dry heat There is great individual variation in the chloride concentration of the sweat but high rates of sweating always lead to hypochloræmia unless the salt loss is replaced (in desert climates men frequently lose as much as 8 or 10 litres of sweat containing up to 20 g of salt in twenty four hours)

Thirst is the principal factor regulating water intake but it does not necessarily reflect the state of hydration of the subject Even experienced and fully acclimatised men working in the heat never voluntarily drink as much water as they lose in the sweat although the deficit may be restored during periods of rest There is no human sensation analogous to thirst which indicates salt deficiency and serious hypochloræmia can occur without the subject being aware of it

Kidney Function—During sweating the kidney helps to maintain water and salt balance by reducing the excretion of these substances The volume of urine may be reduced to about 500 ml per day and chloride may disappear entirely from it although the specific gravity rises on account of an increased concentration of other dissolved substances

Body Temperature—When the subject is exposed to increasing environmental heat both the rectal and skin temperatures rise though at different rates and to a greater extent when work is also done The adaptations already discussed are ultimately concerned in the control

Hot Dry (Desert) Climate—This is characterised by very high dry bulb temperatures (up to about 120° F (48 8° C)) and high solar radiation but low air humidity There is a distinct seasonal variation and several months of the year may be quite cold There is also diurnal variation and even at the hottest time of the year it may be quite cool overnight The sky is usually clear thus allowing free transfer of *radiant energy Sudden and severe windstorms frequently occur* and may be loaded with dust or sand The terrain is characterised by sparse vegetation sand and rocks affording little protection from the heat and increasing the effects of radiation The Sahara Desert the desert region of Arizona and California and parts of Central Australia the Middle East and Northern India are representative of this type of climate

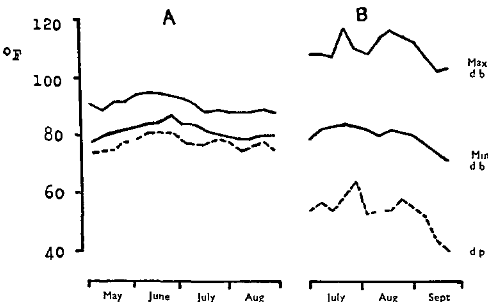


FIG 2—To illustrate the principal differences between jungle and desert climates—(From Horne and Mole 1950) d p = dew point
(A) Jungle Karachi 1946 (original data)
(B) Desert Shaiba 1943 (redrawn from Ladell *et al* 1944)

In a desert climate the stress imposed on the body in its attempt to maintain thermal equilibrium is directed to a great extent on the sweat glands as well as on the circulation During the day the air temperature is constantly much higher than the body temperature and so heat cannot be lost by means of convection and radiation both of which processes will probably add heat to the body Hot winds may considerably increase the heat stress Sweating alone must therefore remove all metabolic as well as accumulated environmental heat Overnight however when the dry bulb temperature may be well below the body temperature heat will be lost without recourse to sweating The clear sky will allow considerable cooling by radiation

Acclimatisation to Heat

The ability of the human body to function properly in a hot environment depends primarily on its ability to adapt its heat dissipating mechanism The limit of tolerance therefore depends also on the limit of adaptability of the two principal factors concerned with this mechanism—the circulatory and sweating systems This adaptability is not fully revealed at the initial exposure to heat, and the optimum response is obtained only after prolonged exposure at levels below the limit of tolerance, or after repeated interrupted exposures By means of this process the body can eventually tolerate environments that would be lethal in the unacclimatised state The acclimatised subject is able to live in a hot environment in reasonable comfort and to work in it with a minimal disturbance of pulse rate blood pressure and body temperature and with an optimal sweating rate Acclimatisation is quite rapidly lost on withdrawal from a hot environment

Studies on acclimatisation carried out in artificial hot environments (such as laboratory hot rooms) have contributed a great deal to the understanding of this phenomenon but they have a limited application to actual life in hot climates One reason is that in a hot climate it is essential that there should also be a psychological adaptation not only to the measurable features of the climate but to all the other immeasurable aspects of the environment associated with the climate—a process for which the word accustomisation has been used The monotony of the tropical climate itself may be an important meteorological factor to be reckoned with in tropical adaptation

Other adjustments also have been made even in skin reflexes for example the gooseflesh reflex has been elicited in individuals long acclimatised to tropical heat when they entered an air conditioned room with an effective temperature of 70° F (21 1° C) which would be quite a warm atmosphere for a temperate climate Even disinclination for physical activity (not allowed for in experimental work) may be a feature of acclimatisation to heat The often criticised lethargy of natives of the tropics at least spares their heat dissipating mechanism and may help to account for the relatively low incidence of heat casualties compared with Europeans There is one factor to which adaptation may be well nigh impossible adequate sleep so essential for general well being and for the successful performance of work may be very difficult to obtain under certain climatic conditions

Types of Hot Environment

Men have to live and work in a large range of hot environments both naturally occurring and artificial and the exact nature of the stress imposed on the body will depend partly on the type of environment There are two contrasting types of hot climate that can be easily distinguished—the dry (or desert) and the humid (or jungle) (Figs 2 and 3)

Hot Dry (Desert) Climate—This is characterised by very high dry bulb temperatures (up to about 120° F (48 8° C)) and high solar radiation but low air humidity There is a distinct seasonal variation and several months of the year may be quite cold There is also diurnal variation and even at the hottest time of the year it may be quite cool overnight The sky is usually clear thus allowing free transfer of radiant energy Sudden and severe windstorms frequently occur and may be loaded with dust or sand The terrain is characterised by sparse vegetation sand and rocks affording little protection from the heat and increasing the effects of radiation The Sahara Desert the desert region of Arizona and California and parts of Central Australia the Middle East and Northern India are representative of this type of climate

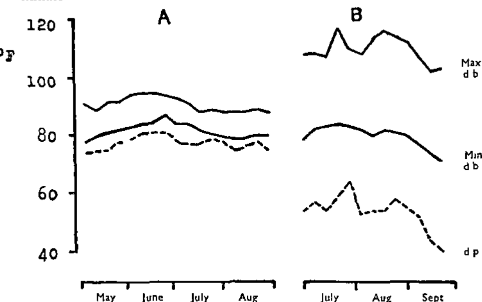


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and blankets may be required for comfort Even when sweating is occurring at very high rates the skin will still feel dry since the low humidity and high air movement allow the evaporation of sweat as fast as it is secreted This may lead to the false impression that active sweating is not occurring Since even when sheltered from the sun the body has heat transferred to it from the atmosphere suitable clothing will reduce heat stress

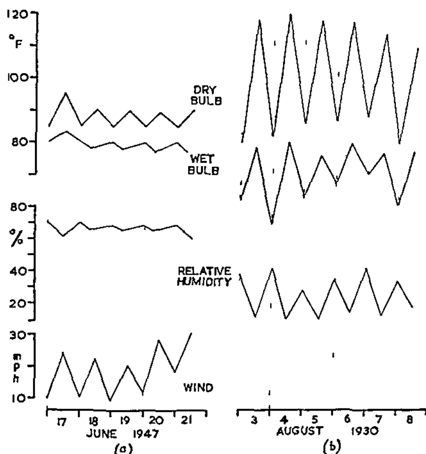


FIG 3 —To illustrate the diurnal variation in different types of climates (at the height of the hot season) The vertical lines indicate midnight
(A) Jungle Karachi 1947 (original data)
(B) Desert Hinaidi 1930 (redrawn from Morton 193)

Hot Humid (Jungle) Climate —This is characterised by relatively low dry bulb temperatures (rarely above 90° F (32 2° C)) and low solar radiation but high air humidity In some areas there is a seasonal variation and several months of the year may be quite cool and dry but more characteristic is the constancy of the climate Also there is relatively little diurnal variation especially during the hotter part of the year and the night may be even more unpleasant than the day Thus a feature of the climate is its monotony The sky is often clouded

and there are frequent heavy showers but these seldom give relief the cooling effect being neutralised by the increased humidity Wind velocities are usually low except for occasional storms and always drop overnight The terrain is characterised by heavy vegetation which serves to retain moisture and increase the humidity Whilst areas having this type of climate are less clear cut than those with the desert type of climate coastal areas of India Malaya and Africa are typical

The stress imposed on the body in its attempt to maintain thermal equilibrium is somewhat different in this type of climate The transfer of heat by radiation and convection may be away from the body and so sweating unnecessary at rest shelter is often available as protection when the heat transfer is the other way When evaporative cooling is required it is limited by the high humidity of the air and air movement becomes an important factor in allowing heat loss The climatic conditions are sometimes such that because of the limited diurnal variation uninterrupted sweating even at rest may occur for weeks on end The high humidity and absence of wind under these circumstances leaves the skin continually wet and this may cause considerable discomfort and even distress The false impression may be gained that a great deal of salt and water are being lost through sweating although the loss is really much less than in the desert The minimum of clothing is indicated for this type of climate

In any one area of course the climate may not conform to either of these extremes and a large range of varying conditions is encountered Artificial hot environments can be similarly analysed and may mimic one or other of these types of climate For example steel foundries may have a very high dry bulb temperature and high radiation temperature with a relatively low humidity stokeholds of ships very high dry and wet bulb temperatures

Influence of Environment on Type of Syndrome Produced

It is now possible to predict the influence of the type of environment on the ways in which a failure of the heat regulatory mechanism will show itself Very high body temperatures and syndromes due to water and salt deficiency will be likely to occur in desert climates with high dry bulb temperatures and high sweating rates The unrelieved sweating and continually wet skin associated with humid climates will produce different effects on the skin and sweat glands from the intermittent (though more profuse) sweating and continually dry skin associated with desert climates A slight degree of impairment of sweating will be more likely to lead to symptoms in a desert climate while inability to sweat at all might even be compatible with life in a jungle climate

Although all hot countries do not have one or other of these two distinct types of climates and considerable mixtures occur there should be a similar correlation between the pathological effects of environmental heat and different parts of the world

Factors Encouraging the Development of Heat Effects Syndromes

It should also be possible to predict the factors which will act as additional hazards and increase the risk of heat casualties occurring in hot environments Experience shows that these factors do act in this way

(*a*) *Lack of Acclimatisation*—Subjects suddenly exposed to hot environments without the opportunity of acquiring acclimatisation will obviously be prone to succumb since the cardiovascular and sweating systems cannot be expected to make the necessary adjustments rapidly enough There have been many examples of this—for instance the large number of heat casualties reported among troops immediately after disembarkation in the tropics and among the civilian population in America during sudden heat waves

(*b*) *Limited Adaptability of Important Systems*—Older people and especially those with cardiovascular disease are notoriously prone to succumb to the effects of heat People with an inadequate number of sweat glands (as for example in the anhidrotic type of hereditary ectodermal defect) are unable to tolerate hot environments Those who are unable to adapt the psyche to a hot environment and its accompaniments will be likely to become psychological casualties

(*c*) *Additional Stress to the Heat Regulating Mechanism*—Heat casualties would be expected to be more likely to occur when subjects are exerting themselves especially if they are not physically fit if they are unsuitably clothed for the heat or work without shade or in badly ventilated premises Febrile conditions and dehydration (as for example in malaria and dysentery) are obviously additional hazards that will lead to an earlier breakdown Excessive alcohol impairs the functioning of the vasomotor system and alcoholics are well known to be prone to heatstroke Prolonged standing will also put an extra strain on the vasomotor system and increase the risk of syncope

Heat Effects Syndromes

The principal clinical features of the syndromes resulting from exposure to environmental heat are excessively high body temperature exhaustion and collapse painful muscle cramps and neurasthenic symptoms The various syndromes will be very briefly discussed under these four headings and a suitable terminology proposed (Table I) This terminology is based on names hallowed by tradition but modified in

TABLE I

A Terminology of Heat Effects Syndromes

Syndrome		Principal Features
Heat Hyperpyrexia		Excessively high body temperature (arbitrarily above 106 F (41 C))
Heat Stroke		Ditto with complete anhidrosis and profound clinical disturbances including delirium or partial or complete loss of consciousness
Heat Exhaustion	Exercise Precipitated	Exhaustion (without dehydration or anhidrosis)
	Dehydration (Hypochloræmic)	Exhaustion dehydration (may be cramps)
	Anhidrotic	Exhaustion chronic anhidrosis
Heat Collapse	Exercise Precipitated	Collapse (without dehydration or anhidrosis)
	Dehydration (Hypochloræmic)	Collapse dehydration oligæmia
	Anhidrotic	Collapse chronic anhidrosis
Heat Syncope		Syncope
Heat Cramps		Painful muscle cramps salt deficiency
Tropical Neurasthenia (Tropical Fatigue etc)		Neurasthenic symptoms

Other Syndromes Heat œdema sunburn prickly heat water deficiency

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TABLE II

A Classification of Heat Effects Syndromes (by Ætiology)

Main Ætiological Factor	Clinical Syndromes
Circulatory deficiency	Exercise precipitated heat exhaustion and collapse Heat syncope
Chloride deficiency	Dehydration (hypochloræmic) heat exhaustion and collapse Heat cramps
Sweating deficiency	Anhidrotic heat exhaustion and collapse Heat hyperpyrexia Heat stroke
Heat regulating centre deficiency	Heat stroke
Psychological deficiency	Tropical neurasthenia etc

Other Syndromes Heat œdema sunburn prickly heat water deficiency

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relatively little physical exertion or even spontaneously The terms *anhidrotic heat exhaustion* and *anhidrotic heat collapse* are recommended for these now well recognised syndromes in which chronic anhidrosis is a feature

The term ***heat syncope*** should be reserved for the classical syndrome (sudden fainting especially after prolonged standing) well known in ordinary environments but obviously more prone to occur when there is the additional strain on the circulation imposed by the necessity for the maintenance of thermal equilibrium in a hot environment Syncope may occur following strenuous exertion in the heat and especially when the erect posture is assumed and maintained after exertion Whilst such a syndrome might be called exercise precipitated heat collapse an exact classification may be difficult and fortunately is relatively unimportant since the treatment of syncopal syndromes is similar

Muscle Cramps —Painful spasms of voluntary muscles may occur following muscular activity in hot environments Their exact mechanism is unknown but they occur when there is salt deficiency and especially after fluid has been replaced without salt Cramps may occur even without muscular activity when salt deficiency is severe The term ***heat cramps*** is suitable for this syndrome provided that it is borne in mind that cramps may coexist with other hypochloræmic syndromes

Neurasthenic Symptoms—Residence in the tropics may have profound psychological effects of a deleterious type sometimes justifying the title of a syndrome which has received various names such as ***tropical neurasthenia*** and ***tropical fatigue*** Morale can compensate only to a limited extent for the physiological stresses of exposure to heat and specific effects such as salt deficiency and inadequate sweating must of course be ruled out before symptoms are labelled psychological It is often difficult to determine to what extent the syndrome is attributable solely to climatic conditions

OTHER SYNDROMES

Heat Œdema—This is the name usually applied to œdema of the extremities commonly experienced in hot climates The alternative name deck ankles indicates that it commonly occurs on board ship in transit to the tropics It is presumably attributable to alterations in the vasomotor system and rapidly clears up with acclimatisation

Sunburn (*Erythema Solare*)—This is a direct result of exposure to sunlight Its importance in a hot climate is that it may contribute to a breakdown of the thermoregulatory mechanism firstly because vasomotor control is temporarily lost over the erythematous areas and secondly because these areas do not sweat and may remain anhidrotic for several weeks

Prickly Heat—This well known condition is of great importance since in addition to the distress it sometimes causes it is followed by

such a way as to indicate the ætiology and clinical features of the syndromes (Table II) It also has the advantage that from it the appropriate treatment can be deduced

Excessively High Body Temperature—The term hyperpyrexia is usually employed arbitrarily when the body temperature rises above 106° F (41° C) When this is due solely to the effects of environmental heat and there are no complicating features it is recommended that the term *heat hyperpyrexia* be used *Heat stroke* should be confined to the classical syndrome—symbolised by the word stroke —in which there are complete anhidrosis and profound clinical disturbances including delirium or partial or complete loss of consciousness and in which the body temperature is usually very high These two syndromes tend of course to merge into each other and the former is frequently a forerunner of the latter

In a hot environment these two syndromes may supervene on a febrile illness and under these circumstances the terms *secondary heat hyperpyrexia* and *secondary heat stroke* should be used in order to indicate that there is an additional pathology Because of the frequent occurrence in tropical climates of febrile illnesses difficult to diagnose it may not always be possible to be certain whether disease has made any contribution to the raised temperature

Exhaustion and Collapse—Some syndromes are characterised by a number of symptoms which together constitute the condition called "exhaustion sometimes severe enough to lead to collapse" in which there is at least partial loss of consciousness Exhaustion and collapse also merge into each other and the former is frequently a forerunner of the latter but they usually differ sufficiently to justify the recognition of two types of syndromes *heat exhaustion* and *heat collapse* Each of these two syndromes can be further qualified in such a way as to indicate the principal mechanism (actually the failure of a mechanism) concerned (Table II) although in some cases mixed ætiologies may be present and it is not always possible to attribute the syndrome entirely to one of them

The symptoms of exhaustion and collapse are due largely to inadequate circulation of the blood and can of course be precipitated in healthy and even well acclimatised subjects as a result of physical exertion in the heat The terms *exercise precipitated heat exhaustion* and *exercise precipitated heat collapse* are recommended for the syndromes when they occur under these circumstances If there is salt deficiency and dehydration exhaustion and collapse will obviously be more easily precipitated by exertion and may even occur spontaneously Under these circumstances the terms *dehydration (or hypochloræmic) heat exhaustion* and *dehydration (or hypochloræmic) heat collapse* are recommended Dehydrating diseases such as dysentery may of course contribute to the syndrome as pyrexial illnesses may contribute to hyperpyrexia and heatstroke

Also if there is anhidrosis these symptoms may develop after

approximately the same number of men were at risk in 1945 there were probably a few cases (the syndrome had not been recognised then) This striking difference in incidence of the syndrome over the three years can be correlated with climatic differences The summer of 1946 was very much more uncomfortable than either 1945 or 1947 although

TABLE III

Incidence of Heat Effects Syndromes in Jungle and Desert Climates

Type of climate	JUNGLE			DESERT
Place	Karachi India			Shaiba Iraq
Source of data	Personal observations			Ladell *et al* (1944)
Year	1945	1946	1947	1943
Number of men at risk (approximate)	at least 6000	6000	5000	not stated
Heat stroke	0	1	0	12†
Heat hyperpyrexia (primary)	unknown	0‡	0	12§
Heat hyperpyrexia (secondary to febrile illness s)	unknown	a few	0	some but no not stated
Chloride deficiency (due to effects of heat)	0	0	0	45
Heat syncope and exercise precipitated heat exhaustion and collapse	unknown	0 30	a few	not stated
Anhidrotic heat exhaustion and collapse— (*a*) complete anhidrosis (*b*) incomplete anhidrosis	few if any	58* 0	2 2	53 (varieties not distinguished but probably incomplete)
Prickly heat	very common but not severe	very common and severe	very common but not severe	fairly common

* Compiled from hospital records and so less complete and less reliable than the other two years.
† Described as hyperpyrexia, b cl all ll w cases f h t trok
‡ One case of anhidrotic heat exhaustion h d an al tempe at e f 06 F (4 C)
§ Described as bo d line hyperpyr ia, with an g rectal temperature of 4 8° F (40·4 C) They resembled hyperpyrexia cas p in th actual h ght f h temperature and b en f mental fus on. The criterion f hyperpyrexia w rectal temperature f 07 F (41 6 C)

the only measurable difference was that the minimum dry bulb temperature and the dew point were a few degrees higher in 1946 (Fig 4) In the outbreak of 1946 the geographical distribution of the cases in the area could also be correlated with small local differences in the climate of the same nature (Horne and Mole 1950) These observations illustrate how relatively small variations in climatic conditions can influence the incidence of heat effects syndromes

varying degrees of reduction of sweating up to complete anhidrosis In anhidrotic heat exhaustion and collapse there is nearly always a history, and sometimes evidence of severe prickly heat

Water Deficiency—Uncomplicated water deficiency resulting from heat stress is uncommon but may occur for example, in shipwreck when survivors may be able to replace salt but not water

Correlation Between Heat Effects Syndromes and Climate and Environment

Various attempts have been made in the past to analyse the distribution of heat effects syndromes in various parts of the world and to correlate them with climatic conditions and with artificial hot environments Whilst it has been possible to draw several general conclusions (such as the gross relation to waves of atmospheric heat, and the great importance of the wet bulb temperature and air movement and of living and working conditions) the results have been unrewarding This is principally because of inadequate data being available and because of the different terminologies in use

There appear to have been only two detailed surveys of all cases of heat effects syndromes occurring in any one place in one or more hot seasons suitable for this type of analysis One is that made by the Medical Research Council team which visited Shaiba Iraq in 1943 (Ladell Waterlow and Hudson 1944) and the other that made by Dr R H Mole and myself at Karachi Pakistan in 1945 1946 and 1947 (Horne and Mole 1950) Both of these investigations were carried out on Service personnel The difference in the climatic conditions between Karachi and Shaiba has already been referred to (Figs 2 and 3) At Karachi even in the hottest part of the three summers the maximum dry bulb temperature was never more than 95 F (35° C) except for a few isolated days in 1947 but there was a very high humidity Karachi, therefore in spite of being on the edge of the Sind Desert had a humid jungle type of climate At Shaiba the climate was of the dry desert type with the dry bulb temperature during the summer ranging from 110° F to 120° F (43 3 C to 48 8 C) and a low humidity

Table III summarises all the cases of heat effects at Karachi in 1945 1946 and 1947 and at Shaiba in 1943 (hospital admissions) At Karachi there was only one case of *heat stroke* in all three years and no cases of *heat hyperpyrexia* (in 1946 there were a few cases of hyperpyrexia secondary to such illnesses as chickenpox as well as malaria) At Shaiba there were 12 cases each of *heat stroke* and *heat hyperpyrexia* At Karachi there were no cases of *chloride deficiency* due solely to environmental heat there were 45 cases at Shaiba

In 1946 there was an abrupt outbreak of *anhidrotic heat exhaustion and collapse* at Karachi 58 cases nearly all of them occurring in the last fortnight of June In 1947 there were only 4 cases although

collapse come from humid areas where prickly heat is also more common and more severe As would be expected, the syndromes of exercise precipitated heat exhaustion and collapse occur in both types of environment and have been reported principally in groups of men doing hard physical work such as soldiers in training and miners In very hot environments these syndromes may be associated with some degree of chloride deficiency Tropical neurasthenia appears to occur more commonly in hot humid climates which are usually of a monotonous character such as West Africa Malaya and Bengal

Conclusion

By studying the way in which the body responds to different types of heat stress it has been possible to clarify the syndromes which result when its heat regulating mechanism fails and it has been shown that even minor variations in environment may lead to important differences in the total and relative incidence of these syndromes The terminology proposed has been based on physiological and clinical principles and it is supported by experience in the field The adoption of such a classification and terminology elaborate though it may seem at first sight is believed to be necessary if the causes of heat effects syndromes are to be understood if the occurrence of such syndromes is to be prevented whenever possible and if the correct treatment is to be applied in the event of their unavoidable occurrence

I am indebted to Dr R. H Mole with whom many of the original observations and investigations were made and who has assisted me in the presentation of the classification and terminology of the heat effects syndromes

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A comprehensive bibliography is included in the author s thesis for the degree of Ph D (Edin) entitled The effects of environmental heat with special reference to anhidrotic heat exhaustion

Since this lecture was delivered a Committee has been formed at the request of the Climatic Physiology Committee of the Medical Research Council and the Registrar General to make recommendations for a new standard nomenclature for diseases due to the effects of environmental heat The report of this Committee is not yet available but it is probable that the nomenclature to be recommended will be similar to that described in this lecture

All of these cases of anhidrotic heat exhaustion and collapse in 1946 were completely anhidrotic two of the four *in 1947* were not At Shaiba the majority of the *55 cases were probably not completely* anhidrotic These observations *substantiate the forecast made earlier* that when there is a high dry bulb *temperature reduction of sweating* short of complete anhidrosis may be associated with symptoms of intolerance to heat

Little information is available about the incidence of *heat syncope* and *exercise precipitated heat exhaustion and collapse* since this type of case recovers rapidly and rarely reached hospital At Karachi it

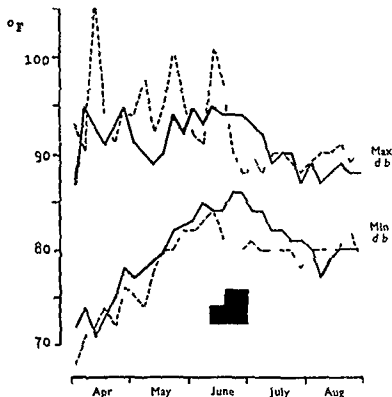


Fig 4—Comparative meteorological data for Karachi 1946 and 1947 (original data)—The *continuous line in each case is 1946* (From *Horne and Mole 1950*)

is known that there were 20 or 30 such cases in 1946 and a few only in 1947 when the troops were less active than in the previous year At Karachi *prickly heat* was always common and moderately severe but its incidence and severity were greatest in 1946 (Horne 1952) At Shaiba it was common and probably fairly severe towards the end of the summer

Interpretation of other published accounts shows *roughly the* same distribution of *heat effects syndromes reports from hot dry* areas emphasise *the importance* of heat stroke and dehydration heat *exhaustion and collapse* reports from humid areas do not On the *other hand,* the majority of accounts of anhidrotic heat exhaustion and

factual measurements are of great value Ideas of the quantity and quality of colour vary a good deal from person to person The difficulty may be illustrated by the term ' bronzed diabetes for hæmochromatosis The composition of ancient bronze ranges from 67 to 95 per cent of copper alloyed with tin zinc lead or silver in varying proportions The bronze of present day copper coinage contains 95 5 per cent copper and the colour of a penny varies with its age and use Bronzed , as a term for the description of colour is therefore open to a very wide interpretation Advanced cases of bronzed diabetes may have a brownish colour with a metallic quality due to deposits of hæmosiderin and increase of melanin in the skin This colour is more familiar as a local condition of hæmosiderosis of the shins so frequently seen in association with varicose veins Many cases of hæmochromatosis do not have this brown colour A common description in the literature is that they show a slatey or a leaden hue Such terms fall prey to a similar temptation to compare with a known substance whose colour can be misinterpreted Leaden refers to the dull dark surface of an old lead pipe and not to the bright silvery metal and in hæmochromatosis it is largely due to increased melanin in the skin

The interpretation of colour in the skin is still further complicated by the physical properties of light For example the dark blue of a tattoo is made by the lampblack of indian ink and the blue occupational tattoo marks of a miner are caused by coal dust while the blue colour of the veins is due to the dark red venous blood within them These effects are due to the rearrangement of light as it passes through a turbid medium That quantity which is transmitted contains a greater proportion of longer wavelengths (red) while the light which is scattered to the sides and back to the surface contains a correspondingly large proportion of shorter wave lengths (blue)

Added to these difficulties it is estimated that 30 per cent of the population have subnormal colour vision [1] Clearly some physical means of measuring the nature the quantity and the distribution of pigments in the skin is a desirable objective The Hardy spectro photometer has been used for this purpose The reflection from the skin of light from a standard source is measured over the whole width of the visible spectrum The pigments present are identified by the appearance of their characteristic absorption bands and the quantity of the substance present is proportional to the degree of absorption of the light Unfortunately the instrument is very costly and its use is time consuming and requires a high degree of technical knowledge and skill The clinical interpretation of results is subject to certain difficulties The phenomenon of scatter already mentioned gives a false colour to pigment lying deeply and melanin in sufficient quantity obscures the absorption bands of other pigments present The instrument takes no account of the clinical features of the patient so that similar results might be recorded for a normal person with a dark

PIGMENTATION

By F B FRENCH

In the white races, especially, abnormal colour of the skin and of the mucous membranes may be a valuable sign in the clinical diagnosis of systemic disease It is proposed here first to consider a few general points concerning normal and abnormal colour, and then to discuss some forms of melanin pigmentation in relation to the biochemistry of melanin formation Many of the known biochemical facts will not be mentioned since they do not yet have any clinical application

A difficult question which arises at once is "What constitutes abnormal pigmentation?" Considerable variations in colour can be appreciated by looking around at any gathering of normal people There may be some with fair hair blue eyes and pink cheeks some with black hair, brown eyes and dark skin and yet others with auburn hair and a pale skin mottled with brown freckles These variations and many others may all be accepted as normal Sudden and extreme variations in colour such as the ghastly pallor which precedes a faint are universally appreciated as abnormal Changes of more gradual onset may not be noticed by patients or by those in intimate contact with them Doctors are equipped by their training and subsequent practice in visual observation to appreciate the abnormal Consultants may have an even greater advantage for they are unfamiliar with the appearance of the patient and first impressions are often the most valuable However an accurate impression depends upon inspection in a good light For instance it may be impossible to recognise even considerable degrees of jaundice in artificial light The complexion of a patient changes just as the colour of dress materials or of lipstick differs in electric lighting or in daylight Background is also important Light reflected from the gloss of a coloured wall may have a profound effect on skin colour Unsuitable conditions for interview commonly suppress or obscure abnormalities of colour The ideal is provided by inspection in indirect sunlight against a light background with a matt surface It is in the familiar circumstances of the well lit surgery or ward that deviation from normal colour may best be appreciated In the assessment there is a subtle integration of the appearance of the skin with the physiognomy and with the colour and form of the hair Physical measurements of hæmoglobin and serum bilirubin give an accurate estimation of colour change in appropriate cases but there are some conditions in which diagnosis by clinical judgment cannot be replaced

For the purposes of description and of recording progress however

Read 3rd December 1953

(2) Variations in blood flow through the superficial vessels will alter the components due to hæmoglobin
(3) Œdema of the skin will cause pallor as in acute nephritis

It is proposed here only to consider melanin pigmentation and some of its abnormalities

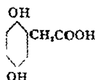
The term melanin is derived from the Greek melas black However the name is applied to a group of widely distributed natural substances responsible for shades of black brown buff and blue frequently seen in plants and animals Melanin occurring in physiological and pathological conditions in man is black or it is tan if it is present in the reduced form If the pigment lies deeply in the tissues it has a blue colour as has already been discussed

Melanins have a high molecular weight and their formation ordinarily depends upon the available concentration of three substances

(1) A suitable phenolic substrate
(2) A phenol oxidase
(3) Molecular oxygen

For example skin melanin is formed from the substrate tyrosine or dihydroxy phenylalanine (DOPA) by the action of the phenol oxidase tyrosinase which is a copper protein complex Pheynlalanine may be converted into tyrosine and both these amino-acids are absorbed from protein digest in the alimentary tract Chart 1 indicates the basic steps by which tyrosine undergoes enzymic oxidation and dehydrogenation and then an unknown degree of polymerisation The transformation into pigment granules requires in addition a physical substrate upon which deposition of pigment particles may take place [3] Protein usually provides this physical substrate

Melanin pigmentation however occurs elsewhere than the skin in certain rare pathological conditions The site at which the pigment is deposited probably depends both upon the type of melanin produced and upon the distribution of the suitable physical substrate For instance in ochronosis there is pigmentation of the cartilages the tendons the ligaments and the scleræ The disease commonly complicates that rare hereditary disorder alkaptonuria The phenolic substrate is probably homogentisic acid



Ochronosis may also result from chronic phenol poisoning due in the recorded instances to the prolonged application of carbolic dressings to varicose ulcers [4] In such cases the substrate is phenol The oxidase is presumably not tyrosinase for this enzyme is found

skin, a case of Addison's disease or a sun bathing enthusiast at the end of a good season Like other ancillary methods of investigation spectrophotometry can provide quantitative and qualitative measurements, which may help to form the final clinical judgment Probably its greatest value has been to elucidate the distribution and the composition of the pigments which are responsible for skin colour in normal and pathological conditions, and to confirm the results previously obtained by histological methods

The normal colour of skin depends upon four components —

(1) Red due to oxyhæmoglobin
(2) Blue due to reduced hæmoglobin
(3) Yellow due to carotene
(4) Brown or black due to melanin and to some extent to melanoid Melanoid is distinguished from melanin only by some absorption of light at the violet end of the spectrum It is found in the stratum corneum and the quantity present runs parallel with the amount of melanin present It is thought to be a product of melanin, and as it has no obvious clinical application, no further reference to it will be made

The colour of the different races of mankind depends upon variations in the quantity of melanin in the skin Red Indians are not a race apart in this respect they derived their name from a custom of smearing their faces with ochre

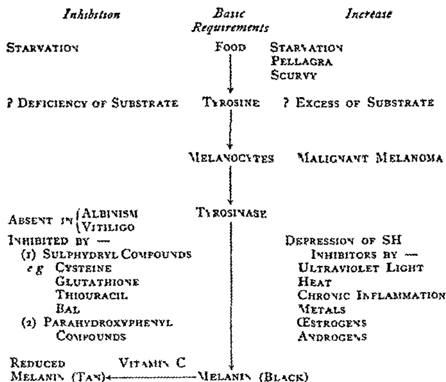
Alterations in skin colour may depend upon a change in any one of the four components or in several of them simultaneously Alterations in colour may also result from other causes

(1) Abnormal compounds of hæmoglobin *e g* methæmoglobin, sulphæmoglobin carboxyhæmoglobin
(2) Yellow pigments such as bile mepacrine and various industrial poisons
(3) Dark pigments such as silver, bismuth and other heavy metals
(4) *Miscellaneous pigmentations e g* associated with malaria porphyria methæmalbuminæmia

Any colours are liable to be modified by certain non specific factors Firstly, there are the effects depending upon the physical properties of light, which may alter some colours more than others These have been mentioned under the discussion of the lighting arrangements and the depth of the pigment beneath the skin Secondly there are anatomical *considerations*

(1) Where the epidermis is thick the skin looks yellower This shows at the greatest extreme over the heel though it is true that here also the carotene content is high Conversely the thin skin of the lip is almost transparent so that the colour of the underlying blood can be seen

Another example of blackish pigmentation with a specific distribution is that which occurs in a proportion of persons taking mepacrine as prophylaxis against malaria[6] The nails of the hands and feet the hard palate and occasionally the nose become brownish black The nature of this pigment is however uncertain but it may persist for many months after the cessation of the treatment



CHART

In the normal human melanin is elaborated by dendritic cells in the basal layer of the epidermis and the hair papillæ and by similar cells in the mucous membranes of the mouth and vagina in the uveal tract and in the leptomeninges There has been considerable confusion in terminology in the past At the Third Conference on the Biology of Normal and Atypical Pigment Cell Growth held at New York in 1951 it was proposed unanimously that these pigment forming cells should be called melanocytes The dendrites of these cells connect with one another to form a syncytium Some of the pigment passes up the dendritic processes into the stratum granulosum but for the most part it is deposited in the dermis where it is taken up by macrophages

Melanocytes originate in the embryo by migration from the neural

only in melanocytes,[3] and melanin formed by them would be expected in normally pigmented areas The suitable physical substrate is found at the special sites of deposition

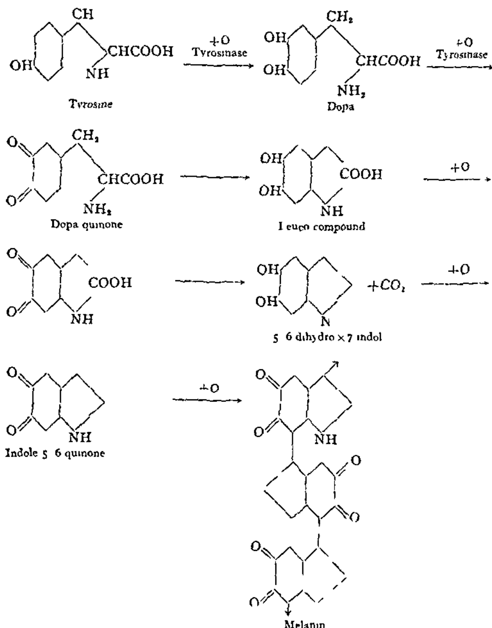


CHART I

There may well be a similar explanation for the remarkable distribution of pigment in melanosis coli The mucosa of the colon looks brown or black, due to the presence of pigment laden macrophages in the submucosa The condition occurs after the prolonged use of excessive quantities of purgatives

and a great deal of almost black pigment inside the cheeks She has been dark skinned for several years yet there has been no proof that she has Addison s disease For some months she has ceased to take Ephedrine but she remains pigmented It is tempting to suggest that Ephedrine acted here as a melanin substrate it would otherwise have to be a remarkable coincidence of two rare phenomena gross pigmentation and ephedrine addiction Incidentally her doctor discovered her addiction when he tried her on luminal without telling her of the change of prescription !

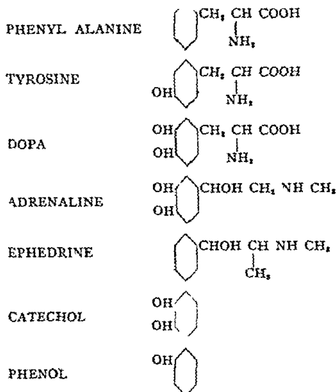


CHART 3

MELANOCYTES

The vast number of melanocytes in occasional cases of malignant melanoma may give rise to generalised pigmentation of the skin multiple pigmented tumours and melanuria There is no reason to suppose that the enormous quantities of melanin produced are not formed from normal sources of tyrosine Doubt is therefore cast upon the idea of an excess of tyrosine ever being the cause of pigmentation On the other hand when an abnormal substrate is present such as homogentisic acid phenol and possibly ephedrine and others it appears probable on clinical grounds that excess melanin formation may take place

crest Several points are reminiscent of their common origin with nerve cells One is their dendritic form and another is the poor response to X ray therapy of the highly malignant melanomata In addition, anomalies of pigmentation may be associated with hereditary or congenital disorders of the nervous system, *e g* neurofibromatosis linear pigmented nævus

There is no explanation for the different distribution of melanin which characterises certain clinical conditions in which the basic mechanism of pigmentation is thought to be the same It should be noted that the inhibitory effect of sulphydryl groups (SH) on the activity of tyrosinase is an important factor in controlling the rate of melanin production Some abnormalities of melanin pigmentation of the skin and mucous membranes will be considered in relation to the biochemistry of melanin formation as indicated in Chart 2

Food

Both depigmentation and pigmentation are found in association with starvation[6] Lack of protein might result in shortage of tyrosine and tyrosinase and it has been suggested that vitamin deficiency (? pantothenic acid) may also be responsible for deficient pigment formation Similarly protein lack might result in tissue shortage of cysteine and glutathione with consequent pigmentation Inflammation depresses the inhibitory effect of sulphydryl groups and may account for the pigmentation of pellagra In scurvy the explanation may be that all melanin is present in its black oxidised form, owing to lack of the reducing action of ascorbic acid More observations are required before the complex effects of starvation can be separated

Tyrosine

This amino acid is obtained from protein digestion or it can be made in the body from phenylalanine In other words the latter is also a substrate for skin melanin In addition to these two compounds a large number of naturally occurring phenolic substrates are known The pigment formed from them is not always identical with skin melanin A few of these substances are listed in Chart 3

Of these ephedrine and phenol are not proven substrates but they have been inserted to show their chemical similarities to the other substances and because of their possible clinical implications

The position of phenol in relation to the development of Ochronosis has been mentioned Ephedrine is included because of a remarkable case shown by Professor Dunlop at a meeting of the Heberden Society on 10th May 1951

A woman of 39 years became addicted to Ephedrine which she began to take at the age of 20 because she thought she had asthma She would tip from the bottle as many as 30 half grain tablets and swallow them all at once She had been accustomed to this dose for at least five years The patient has dark hair brown eyes dark skin

hands and arms [8] The affected areas corresponded exactly with the length of rubber gloves worn in the course of their work Some of them also showed a patchy loss of pigment elsewhere on the body The cause of their complaint was traced to benzyl ether of hydro quinone used as an antioxidant for the preservation of the rubber gloves It can be used as an ointment in the treatment of freckles chloasma Addison s disease or other forms of melanin pigmentation Recommended strengths have varied from 1 to 50 per cent but a 5 per cent ointment applied every morning and evening has recently been preferred as the optimum concentration Skin hypersensitivity has rarely been encountered and then only after several months treatment Perhaps this difficulty will be overcome if the recent trials of the drug by mouth fulfil their initial promise [9] The following case is an example of the use of the drug

A woman of 55 was seen on 24th January 1949 Addison s disease was suspected on account of her main complaint of asthenia and of the presence of faint ill defined brown areas of skin on the upper part of her back and pigmentation of an abdominal scar The blood pressure was 145 100 Biochemical investigation proved negative and she was not seen again for eighteen months By then her skin and the mucous membranes of the mouth and vagina were grossly pigmented her blood pressure was 80 50 and all the biochemical tests for Addison s disease were positive In spite of adequate treatment with DCA the skin became progressively darker and caused her great embarrassment Neither treatment with ascorbic acid 500 mg b d by mouth for two months nor with 1 per cent hydroquinone ointment for one month caused any lightening of her colour Sub sequently she was maintained in excellent health by additional treatment with 12½ mg cortisone by mouth daily but her pigmentation was unaffected After four months treatment with 20 per cent benzyl ether of hydroquinone in Ung Aquosum B P her skin has become very much less black and somewhat pinker Such a colour change could be measured accurately with a spectrophotometer but in her case it is so obvious that her friends are commenting upon it It has also been checked by repeated water colour paintings and by colour photographs both of which methods show a great improvement After rubbing in the ointment crystals are left on the skin and this tendency can be reduced by making a paste with the crystals in ether before mixing them with the base

TYROSINASE

Factors Increasing Melanin Formation

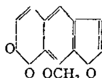
Increased melanin formation occurs if the inhibitory action of sulphydryl compounds is reduced This may result from several separate or combined causes

1 *Heavy Metals*—Pigmentation may occur when heavy metals such as arsenic bismuth, iron gold silver and mercury are deposited

TYROSINASE

Factors Decreasing Melanin Formation

In albinos and in the depigmented skin of vitiligo melanocytes are present in normal numbers, but they contain no tyrosinase It has been reported that pigment returns to the affected areas of vitiligo in many cases as a result of local or oral treatment with 8 methoxy psoralen [7]



A crude extract for external application derived from plant sources has been used by the natives of Egypt since the thirteenth century The active principle was isolated in 1948

The enzyme action of the copper protein complex tyrosinase may be inhibited by substances containing sulphydryl groups and by parahydroxyphenyl compounds

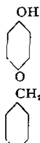
(1) *Sulphydryl Groups*—In normal circumstances cysteine and glutathione play this part and these substances can be demonstrated in high concentration in white skin Oral cysteine is reported to decrease the pigmentation of Addison s disease [3]

Thiouracil is an example of a therapeutic substance which has a similar effect Given to a case of malignant melanoma with melanuria it has been shown to decrease the concentration of melanin precursor in the urine [3]

It is interesting that thyroid hormone is derived from tyrosine for patients with hyperthyroidism are sometimes pigmented Treatment with thiouracil may restore both features to normal while in one instance a negro developed areas of depigmentation while under treatment [3]

BAL may also reduce pigmentation especially that in relation to chronic arsenic poisoning

(2) *Parahydroxyphenyl Compounds* —Benzyl ether of hydroquinone is the best example



Clinical interest in this substance was first aroused in 1939 when negro workers in a factory claimed damages for depigmentation of the

of some common diseases which may be seen abroad Pigmentary changes are present also in a number of conditions which are primarily of dermatological interest Of these acanthosis nigricans in its malignant form is unique and it deserves special mention

Acanthosis nigricans is characterised by pigmented, warty excrescences in the axillæ and other body folds There are benign and malignant forms The benign form has an early onset even from birth It progresses at first especially at puberty and later declines or remains stationary

'Malignant' acanthosis starts at any age but most commonly in adults It is always associated with widespread adenocarcinoma and in 70 per cent of cases this arises in the stomach The tumour may precede accompany or follow the onset of the skin lesion At autopsy 50 per cent have suprarenal metastases but no clinical or biochemical evidence of suprarenal involvement has ever been detected

In conclusion it must be admitted that a number of British patients with dark skin brown eyes black hair and pigment in the mouth are seen in whom no pathological cause of the pigmentation can be found No intermarriage with a dark skinned race can be traced in their ancestry Pigmentation in the mouth has been said to be almost pathognomonic of Addison s disease If this diagnosis is suspected on clinical grounds it is true that the finding of pigmentation in the mouth almost clinches the diagnosis If however the mouth is inspected critically in every patient the presence of pigmentation is nothing like as rare as Addison s disease

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[9] Lerner A B and Fitzpatrick T B (1953) *Journ Amer Med Assoc* 152 580

[10] Brinton W D (1949) *Guy s Hosp Rep* 98 88

in the skin How much the metals themselves are concerned with the skin colour is very difficult to say but the clinical features will often distinguish between these metals Bismuth and mercury may be associated with stomatitis and a blue line along the gum margins Arsenic gives a diffuse brown colour mottled by depigmented areas the so called *rain drop appearance* There is *evidence that metals in* sufficiently high concentration may act by competition with copper in the formation of tyrosinase Such competitive inhibition may explain the depigmented areas in chronic arsenical pigmentation Hyper keratosis of the palms and soles is a confirmatory clinical point in diagnosis In argyria, the colour has a more metallic appearance than simple melanin pigmentation and the areas exposed to light are strikingly affected If a covered area is exposed to ultra violet light a subsequent greyish pigmentation remains for at least a year [10]

2 *Ultra Violet Light*—Exposure to natural or artificial ultra violet light is followed by a variable degree of sun tan

3 *Heat*—For instance erythema ab igne occurs on the shins and a similar mottled pigmentation may result from the frequent application of a hot water bottle

4 *Chronic Inflammation*—For example pigmentation occurs in eczema, or after X ray therapy

5 *Hormones*—Œstrogens inhibit SH groups If given by mouth *to young women they result in darkening of the areolæ and nipples* of the linea abdominalis and of moles Local application has a similar result No such effect is produced after the menopause It is probable that the chloasma of pregnancy is produced by œstrogens

Similar effects are produced by androgens Eunuchs fail to develop a sun tan but if they are given testosterone their skin responds normally to sunlight

Finally there is a group in which the mechanism of pigmentation remains unexplained Foremost among these is Addison s disease It has been suggested that with the loss of the adrenal medulla tyrosine which is no longer required to form adrenaline is converted into melanin *Against this simple suggestion are the facts that pigmentation occurs* in atrophy of the suprarenal cortex with the medulla intact It does not occur in hypoadrenalism accompanying Simmond s disease nor does it follow denervation of the suprarenal medulla after sympath ectomy although there is evidence that adrenaline is no longer secreted in response to stress It is probable that the cause of the pigmentation *is to* be sought in the unopposed action of some pituitary hormone

Pigmentation of the skin and the mucous membrane of the mouth resembling Addison s disease may accompany cachexia due to malignant disease reticulosis tuberculosis and other chronic diseases It occurs also in the malabsorption syndrome and in cases of pernicious anæmia accompanied by diarrhœa

It would be *possible to* add a list of rare disorders associated with a disturbance of melanin pigmentation occurring in this country and

placed these necessities beyond the resources of the average private individual Thus the day is not far off when our own Health Services will be forced also to shoulder this additional responsibility—a responsibility which entails not only the management of established cases but the even greater problem in preventative medicine

The incidence of cerebral palsy varies with different authorities The American figures based largely on the vast clinical experience of Phelps suggest that seven children per 100 000 of the population per year are cerebrally palsied Of these one will die before the age of six to eight years but the other six will live a normal span In this country Dr Keddie and Dr Holloran place the incidence in

TABLE I

CEREBRAL PALSY	SPASTIC	Monoplegia		1
		Hemiplegia	Left	10
			Right	13
		Paraplegia		8
		Triplegia°		8
		Quadriplegia		24
	ATHETOID			20
	TREMOR AND RIGIDITY			5
	ATAXIA			-
	MIXED			9

the school population at about 1 to 2 per 1000 If all ages were considered and minimal handicaps recognised it is probable that these last figures might be higher The problem however is not a static one but one which increases with the population year by year so that in America at least it is considered to be second in importance only to that of poliomyelitis

Cerebral palsy is essentially a neuromuscular disorder due to damage to disease or developmental defects of the brain which may occur before during or after birth The picture is frequently complicated further by associated defects of speech sight hearing intelligence and emotional stability

In a recent analysis of 100 cases of cerebral palsy (Table I) the frequency of the various forms are shown and the distribution of the physical handicap demonstrated The classification which is favoured by The American Academy of Cerebral Palsy adds to the types shown in Table I two additional but rare forms—the high spinal spastic and the aspastic spastic (Table II)

SOME ASPECTS OF CEREBRAL PALSY

By GEORGE A POLLOCK

WERE I to chose a text for this paper I doubt if I could find one more appropriate than that in the Acts of the Apostles Chapter III, and at the second verse —

> And a certain man lame from his mother s womb was carried whom they laid daily at the gate of the temple which is called Beautiful to ask alms

The context makes it reasonably clear that he was a case of paraplegia who craved alms at the gate of the temple To the best of my knowledge this is the first medical reference to cerebral palsy Sixteen hundred years were to pass before Shakespeare dramatised the condition in the person of Gloucester in *Richard III* You will recall the words of that description —

> I that am curtail d of this fair proportion
> Cheated of feature by dissembling nature
> Deform d unfinish d sent before my time
> Into this breathing World scarce half made up
> and that so lamely and unfashionable
> That dogs bark at me as I halt by them

How poignantly descriptive is that passage how bitterly does it draw attention to his deformity Prematurity developmental defect and even anoxia can be read into the lines Time still rolls on and to our shame it must be confessed two hundred years were still to pass before Little penned his classical descriptions in 1843 and 1862 In these two erudite papers Little left little or nothing for us to add to day in elaboration of the clinical picture of etiology

In this country the next events of importance were the establishment in 1946 of The Scottish Council for the Care of Spastics followed within a few days by the birth in London of The British Council These two Societies were the direct outcome of events in America where some thirty five years ago Bronson Crothers of Boston followed by Phelps of Baltimore developed and extended the physiotherapeutic approach to the problem of cerebral palsy

They in turn have been brilliantly supported since by the clinical efforts and experimental researches of Carlson—himself a spastic and internationally known specialist in cerebral palsy—of Temple Fay Perlstein and others and *to such good effect* that to day there are few if any States in the Union without a cerebral palsy clinic supported by State or Federal funds The high cost of medical management and of educational and vocational training of the spastic has already

Read 4th June 1953

which may be rapid or slow coarse or fine and are aggravated by voluntary efforts The rigidity case shows certain of the stiff features of the spastic but is differentiated from the latter by the absence of alteration in the deep reflexes and by the characteristic feel of the limb when it is exercised passively Passive extension of the elbow may take place with a cogwheel like character or it may give way gradually as does a lead pipe hence, the terms lead pipe and cogwheel rigidities In other cases the rigidity appears to pass off for no known reason to appear again in an equally unaccountable manner—constituting a third intermittent form

Aspastic Spastic

The aspastic spastic is one in which the lesion is considered to involve Area 4 (Brodmann s classification) only Only certain muscles are affected and they show the characteristics already described They are the alienated or zero cerebral muscles of American literature muscles which do not atrophy although they do not contract voluntarily This type is exceedingly rare and I have observed these characteristic findings in the anterior tibial muscle alone and in only a few spastic cases

High Spinal Spastic

The high spinal spastic is caused by a subluxation of the odontoid process during the delivery of the aftercoming head of a breech presentation or occurs as the result of an accident after birth The odontoid processes dislocates backwards to cause pressure over the decussation of the pyramids in the medulla and so gives rise to a typical quadriplegic spastic paralysis

Athetoids

It is in regard to the athetoid cases that I should like to speak particularly to day In my first analysis these represented 20 per cent of the cases reviewed For the purposes of this paper I have reviewed 30 athetoids who have been under observation for at least one year (Table III) These children are remarkable for the purposeless

TABLE III

30 *Cases of Athetosis*

Males		21	*Females*		9
I Q over 80 (4 over 100)		13	I Q under 80 (8 not estimable)		17
Handedness	R 13		L 14	Ambidextrous	3
Birth Sequence	1st—14		2nd—8	1 was Ninth	

involuntary and inco ordinate movements of their limbs which usually affect the muscles of expression also and when this is associated with a marked drooling of saliva and poor to absent speech it is not surprising that many were considered to be mental defectives The

SPASTICS

The spastic child is a stiff child to whom every voluntary movement is an effort It is characterised by exaggeration of the deep reflexes the presence of a positive Babinski test with ankle and patellar clonus but the diagnostic sign is the "stretch reflex" which is elicited by any sudden voluntary or passive movement As the result of such an act, the excursion of the joint movement is arrested at a definite point by spasm of the spastic muscle this is known as the threshold of the reflex Not all the muscles of the spastic case are spastic some are normal others particularly those opposing the spastic group are weak while others again depending upon the presence of a lesion in Area 4 (Brodmann's classification) may be so alienated that they cannot be made to contract voluntarily One characteristic feature

TABLE II

Classification of Cerebral Palsy

Spastic
Athetoid
Ataxia
Mixed
Tremor and Rigidity
Aspastic Spastic
High Spinal Spastic

is that although these muscles appear to be paralysed they do not atrophy and they can be trained to contract by overflow and con fusion movements

The spastic child is a rather introspective individual who is sensitive to criticism and of failure on his own part to progress normally He is frequently considered to be reserved and lacking in affection but this is a protective pose to save himself the pain caused by muscle spasm so frequently produced by any demonstration of affection Mental retardation to the point of mental deficiency is present in a high proportion of these cases not more than 50 per cent in my series were educable

ATAXIA

The drunken staggering gait of the ataxic child is characteristic and need only be seen to be easily recognised The deep reflexes are normal or even depressed since the general muscle tone of the ataxic patient is poor The characteristic pendulum like movement of the knee jerk is also found only in cases of this type Nystagmus loss of muscle joint sense and a positive Rhomberg test may be found on clinical examination and the presence of defects of speech are common

TREMORS AND RIGIDITY

These form but a small proportion of the cases of cerebral palsy The tremors localised or generalised are flexion extension movements

in the neck and arm If we flex one arm and extend the other elbow the patient s head turns towards the outstretched hand so that we really have got what amounts to a tonic neck reflex Dr Phelps speaks of these children as having educated feet they can draw write crochet or pull off and on their socks with their toes They may have a hearing defect also and talk poorly but this latter is probably due to athetoid movements of the tongue muscles etc There was only one example of this type in my series

The *deaf athetoid* is a very characteristic clinical entity All have large expressive eyes and all are automatic lip readers Inability to raise the eyes upwards without moving the head also or to wrinkle the brows is a notable clinical observation The hearing defect is a tonal one which occurs between 1000 and 4000 cycles The children are unable to appreciate the S Th and F sounds Their audiograms demonstrate a characteristic fall from 1000 which only begins to rise at a little over 4000 This type of tracing may be seen also in congenital defects of the cochlea The hearing defect is bilateral both ears being within 10 degrees of each other As children from 3 to 6 absorb sound like a sponge to form auditory memories and pathways it is essential that this condition be recognised and treated early If treatment is delayed beyond the age of 14 the period of extreme receptivity has passed and bad patterns have been formed already since the child has had to struggle along without hearing or appreciating the difference between certain consonants Early recognition and treatment with hearing aids while not perfect will probably permit of retention of 80 per cent of function but if untreated until 14 recovery will probably not exceed 20 per cent Many of these children have excessive pharyngeal lymphoid tissue overgrowth which may partially block the eustachian tube and lead eventually to a lowering of appreciation of the low toned consonants also so that even ordinary speech snapping of fingers etc ordinarily appreciated by the deaf athetoid are lost All cases of this type should be seen by an otolaryngologist alive to these possibilities so that the condition can be dealt with surgically without delay

Hemi athetosis is seen usually at the Out Patient Clinic since these children are capable of doing for themselves The athetosis as the name suggests is limited to one half of the body

The *cerebellar release athetoid* can be likened to the reaction of the ordinary individual as he walks in a rapidly travelling train He will overcorrect his tendency to fall to one side by lurching violently to the other This over action on the part of the cerebellum can be partially corrected by the administration of cerebellar depressant drugs such as dilantin or alcohol

The *emotional release* type is characterised by a lack of emotional control thus laughter tears and anger are always near the surface and can be evoked easily The sudden release of inhibitions may annoy the patient but it is outwith his control The brakes seem to

excessive movements are aggravated by excitement and by attempts at purposeful movements They usually involve the entire body but occasionally may be limited to one side only They are absent during sleep, or during periods of intense concentration such as while reading or looking at an interesting movie They disappear during anæsthesia and it is interesting to note that during the stage of recovery many speak almost clearly unhappily as consciousness returns to normal the intelligibility of the speech as rapidly deteriorates As a general rule, the deep reflexes are normal although occasionally a positive Babinski or ill sustained ankle clonus may be elicited The stretch reflex however is absent As the muscles of the athetoid are normal it is generally accepted that the error whatever it may be lies at a higher level and is probably in the nature of lack of synchronisation In this we have almost certainly the explanation of the poor results which have followed tendon transplantation etc

Temperamentally the athetoid is a happy go lucky child who unlike the spastic is prepared to laugh at his failures and to try again Since the lesion in athetosis was supposed not to involve the cortex it was believed in the past that the athetoid was more intelligent than the spastic child but this has not been my finding The educability of the athetoid is no greater than that of the spastic as a whole, although the probability is that certain members of the athetoid group may have a higher degree of intelligence

Phelps Classification of Athetoids into 12 main groups is based on certain characters of manner of movement or of muscular state and while of very considerable interest is probably only of descriptive importance 1 Non tension 2 Tension 3 Head neck and arm 4 Deaf 5 Hemi athetosis 6 Cerebellar release 7 Emotional release 8 Rotatory 9 Tremor 10 Shudder 11 Flail 12 Dystonic

The *non tension athetoid* is one in which the inco ordinate involuntary and purposeless movements have full play so that the limbs may fly about in all directions without any successful attempt being made at control

The *tension athetoid* is one in which according to Phelps an attempt on the part of the patient to control his excessive movements leads to increased tension in the muscles so that the limbs become stiff and may even suggest spasticity There is however no stretch reflex As a result of this tension the muscles hypertrophy abnormally so that these children may become phenomenally strong thus when excited it may take several men to hold the patient and apply his braces The author has observed a similar degree of tension in an infant and at an age when attempted voluntary control of the movements was unlikely and who eventually developed all the characteristics of a quadriplegic tension athetoid This was by far the commonest type in this series

Head neck and arm—The athetoid movements are more marked

Unskilled obstetrical care was for long considered to be the principal factor in the causation of cerebral palsy There is no doubt that many cases of cerebral palsy do date from birth but probably less than 10 per cent are attributable directly to faulty and unskilled obstetrics

A long difficult labour may result in damage to the skull and underlying brain from excessive moulding of the skull and lead to tearing of the cortical vessels with hæmorrhage and injury to the brain surface where neither drugs nor instruments have been employed Excessive or ill advised anæsthesia such as spinal etc may lower the blood pressure to a dangerous level for the child and result in diminished oxygen supply to the brain A breech birth adds to the hazards of anoxia those of damage to the Vein of Galen from traction on the aftercoming head Pinching of the cord between the pelvic brim and fœtal head or torsion round the neck may also cause anoxia with petechal hæmorrhage in the brain substance Sudden pressure changes during a precipitate or Cæsarean delivery not infrequently result in a spastic paraplegia from a subfontanelle cortical hæmorrhage —developments often outwith the control of the practitioner but not all beyond his skill to anticipate and perhaps even correct To these potential active causes may be added the predisposing factors of prematurity primigeniture race and sex

In the report of the Registrar General for Scotland in 1948 106 children died at birth from brain injuries of which number 67 were males In my figures 68 per cent of cerebral palsied patients were first and second births (49 per cent were first children) It would *appear therefore that the male child particularly if he is the first* born runs a greater risk than the female of cerebral damage

Race also exercises an influence but the explanation is obscure It is generally accepted however that cerebral palsy is commoner in the white race than in the black and is least frequent of all among the orientals

PATHOLOGY

For teaching purposes it has been assumed that lesions affecting the pyramidal tracts subcortical regions and the precentral gyrus give rise to spasticity that those found in the basal ganglia and their connections are responsible for the symptoms of athetosis tremors rigidities and dystonia—the picture varying with the precise area affected and that ataxia follows upon similar affections of the cerebellum its connections and the eighth nerve

This simple geographical pattern no longer meets every case since certain patients clinically considered to be examples of extra pyramidal rigidity were found pathologically to show evidences of an aplasia of the cerebellum and others which demonstrated during life features of athetosis at necropsy showed evidence of cortical damage only (Infantile Cerebral Palsy *Journ Amer Med Assoc* 3rd May 1952 vol 149 pp 30-34 M A Perlstein) The author

be off In spite of all appearances to the contrary, the patient may not be greatly upset emotionally

Rotatory athetoid—In this condition the movements are rotatory, so that the shoulders are rotated usually inwards It differs from the tremor athetoid in that there is no flexion or extension movement

The *tremor athetoid* shows a reciprocal action of antagonistic muscles in which there is flexion and extension of the joints The tremor may be fast or slow, gross or fine

Shudder—Phelps likened this to dropping a piece of ice down the patient's neck The shudder may be slight or it may be so severe that the patient falls down The condition is not constant but occurs every few minutes so that the patient may be afraid to walk unsupported The application of braces will prevent a child falling and will give him confidence to walk alone

Flail—Dr Phelps admits that this is a poor term The limbs are thrown about in a flail like manner the proximal joints being those principally affected with very little movement taking place in the more distal ones

Dystonic—In this condition the patient assumes distorted postures from time to time holding each for a few minutes before a totally different attitude is assumed The trunk muscles are tense and more involved than are those of the limbs The cause is not known The dystonic type resembles dystonia musculorum deformans which usually comes on about the sixth year and almost always begins with a weak or swollen ankle This form was met with only once in the series reviewed

Etiology

The concept that those factors which give rise to cerebral palsy may act before, during or after birth has had a more or less general acceptance

The post natal group is clear cut and well recognised but this cannot be claimed with the same assurance for the other two, as it is virtually impossible clinically to differentiate the pre natal from the natal form at birth

An injury to the head of the infant during parturition sufficiently severe to give rise to concern for its survival may clear up in an astonishing way leaving little if any obvious sequel in the form of emotional or mental instability or spastic defect

We are also equally and unhappily familiar with the apparently normal infant born spontaneously and without incident to young healthy parents of unimpeachable family and personal histories who later on develops all the stigmata of a severe cerebral palsy

There is a growing weight of evidence to suggest that developmental defect virus infections Rh factor anomalies and perhaps even endocrine dysfunction and toxic influences during pregnancy may have an etiological significance greater than has as yet been accepted

healthy or was a bit slow but would be all right in time Stiffness of the limbs discovered at bathing time difficulty in putting on nappies unnatural quietness of the child or the presence of a squint and as the months pass delay in reaching the usual developmental milestones in time all call for fuller investigation and not for reassurance

TREATMENT

Drugs —There is no drug which will cure or permanently lessen the disabilities of this condition Anticonvulsant drugs are of benefit but only in so far as they control the frequency or severity of the convulsive seizures Perhaps alcohol alone of all the drugs has the most immediate marked but unfortunately only temporary effect

Surgery —Lumbar puncture or repeated subdural tap through the anterior fontanelle followed by craniotomy as advised by A N Guthkelch of Manchester may result in a cure but once the clinical features are established there is no curative surgical procedure known to day Cordotomy in severe athetosis or hemispherectomies in certain hemiplegias have their advocates but the number of cases so treated is still small and a sufficient period of time has not yet elapsed to permit of a balanced opinion

In the rehabilitative field orthopædic surgery has a contribution to make and much benefit has resulted from the surgical fusion of wrist knee ankle and subtaloid joints in both spastic and athetoid cases Muscle lengthening and transplantation in the spastic group has been of benefit but is almost always an unqualified failure in the athetoid This is not unexpected since in the athetoid case the muscles are normal—it is the integration of movement which is at fault—a condition which will not respond to peripheral surgery Correction of contractures and deformities are still possibly required but earlier diagnosis and preventative care should in time render such procedures unnecessary

In the established case of cerebral palsy the role of surgery is to prepare the way for physiotherapy and occupational measures of rehabilitation In the physiotherapeutic treatment of the cerebrally palsied child the first essential in the case of the athetoid is to obtain relaxation and in the spastic to work through and overcome the stretch reflex

Relaxation is obtained by (1) Jacobson Method or (2) by the visuo kinæsthetic method we practise at Westerlea Once this is obtained muscle co ordinated patterns of movement are developed by the Temple Fay technique

Sooner or later a decision must be taken in regard to education We at Westerlea in our initial screening gauge the intelligence level in terms of I Q

Those children who are educable or have an I Q over 80 have equal rights with the normal child to an education even we believe if it provides him in the future with only personal solace For the

can recall one typical case of athetosis who succumbed to an inter current infection and in whom no pathological signs were found in the brain. Phelps reported a case of athetosis some time ago in which the basal ganglia were found to be absent at the post mortem examination

In general developmental defects of the brain result in symmetrical bilateral lesions of the body and limbs while unilateral involvement of the body is almost always secondary to a destructive lesion such as a hæmorrhage, inflammation, or a tumour (Josephy)

DIAGNOSIS

The earlier cerebral palsy is diagnosed and the sooner treatment is begun, the better the prospects of successful rehabilitation The experienced physician should be capable of establishing the diagnosis in almost every case within the first year of life and in many long before this While it is important to reach an accurate diagnosis early for the sake of treatment there are other sociological implications perhaps of greatest moment that of adoption In the last month the author has been consulted by the parents of two separately adopted children both of whom were severely handicapped by cerebral palsy Although a clean bill of health had been provided in good faith by the authorities concerned in the adoption enquiry subsequently elicited a far from satisfactory birth history Both children had been born limp and blue after a difficult labour and both for several days in the neo natal period had required constant care Such a history should have called for a skilled medical examination prior to adoption and had this been available the early signs of the condition could have been noted and considerable heartache prevented

The most important factor in early diagnosis is a careful and full story of the family and personal histories of the parents with particular regard to the pregnancy of the mother Full details of the birth and of the early neo natal period must be recorded and should be available for reference A prolonged labour even if it terminates spontaneously may be of significance resuscitation measures post natal irritability or drowsiness, bulging of the anterior fontanelle and muscle twitching even where an apparent recovery to normal takes place before the child is discharged from hospital should arouse suspicion and call for repeated medical review at three monthly intervals for the first eighteen months of life before the child is considered to be normal This is particularly necessary where jaundice due to Rh incompatibilities has been present It is imperative that these routine examinations be carried out by experienced physicians and of almost equal importance is that the impressions of the grandmothers be not ignored or dismissed as of little account In almost 20 per cent of my cases reference to the family doctor and to the hospital had been made by the parents at the instigation of the grandmother and as early as the third month yet in such instances the parents were assured that the child was

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highly intelligent a University career may be possible but this should be provided only if there is a possibility of its being put to good use A good degree or a high intelligence in the presence of a severe physical defect as in the athetoid may lead to frustration and suicide if a job cannot be obtained Therefore, not only the athetoids, but the general public must be educated to their responsibilities with regard to these handicapped children For those to whom the gates of learning are closed contentment and a sense of personal worth may be obtained by training in routine skills in gardening or farming etc While for those whose disabilities preclude even such limited activities sheltered workshops or residential institutions for permanent care must be provided to which the stigma of the old asylum must not be attached

POSTSCRIPT

(*a*) Spastic
(*b*) Athetotic
- (i) Tension
- (ii) Non tension
- (iii) Dystonic
- (iv) Tremor

} Types of Athetosis acceptable to the Academy to date

(*c*) Rigidity
(*d*) Ataxic
(*e*) Tremor
(*f*) Atonic
(*g*) Mixed

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R T D I GREAT RI A N Y O AND U T E